Economic impact of postoperative delirium – Detection of risk factors for further prevention program

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List of abbreviations

ASA	American Society of Anaesthesiologists
DGAI	Deutsche Gesellschaft für Anästhesiologie und Intensivmedizin
DRG	Diagnosis-related groups
ESAIC	European Society of Anaesthesiology and Intensive Care
GBA	Gemeinsamer Bundesausschuss
ICD	International Statistical Classification of Disease and Related Health Problems
ICU	Intensive Care Unit
InEK gGmbH	Institut für das Entgeltsystem im Krankenhaus
IQTIG	Institut für Qualitätssicherung und Transparenz im Gesundheitswesen
LOS	Length of stay
mHELP	modified Hospital Elder Life Program
NYHA	New York Heart Association
MoCA	Montreal Cognitive Assessment
PCCL	Patient Clinical Complexity Level
POD	Postoperative delirium
PROPDESC by	PRe-Operative Prediction of postoperative DElirium appropriate SCreening

1. Abstract

Introduction

Postoperative delirium (POD) is an underdiagnosed and adverse complication in older adults. The aim of the PRe-Operative Prediction of postoperative DElirium by appropriate Screening (PROPDESC) study was to develop a pragmatic screening risk score for POD. Furthermore, the medico economic outcome was examined in the additional subgroup analysis.

Methods

The prospective observational monocentric study enrolled 1097 patients from Sept. 2018 to Oct. 2019 in the University Hospital Bonn. Inclusion criteria were patient aged 60 years and older and a planned surgery duration of at least 60 minutes. The primary endpoint POD was considered positive if any of the following tests were positive on any of the five postoperative visit days: Confusion Assessment Method for ICU (CAM-ICU), CAM, 4'A's Test (4AT) and Delirium Observation Scale (DOS). The development and validation of the risk score is based on data-driven approaches to model generation, a boosting process. Multiple logistic regression model was performed for multivariate analysis.

Results

The selected and simplified PROPDESC score with an AUC of 0.725 includes the following variables: age, ASA and NYHA classification, surgical risk as well as ´serial subtraction´ and ´sentence repetition´ of the Montreal Cognitive Assessment. The results of the logistic regression for patients aged 70 years and older showed POD as an independent predictor for a prolonged length of stay (LOS) in Intensive Care Unit (ICU) (36 %; 95 % CI 4–78 %; < 0.001) and in hospital (22 %; 95 % CI 4–43 %; < 0.001). Furthermore, in the cardiac surgery subgroup, the number of POD patients testing positive differed substantially from the coded POD diagnoses in Hospital and the Germany-wide average.

Conclusion

POD showed an independent effect on LOS in ICU and hospital and, moreover, it is highly underdiagnosed in clinical routine. The PROPDESC score, which can be collected in a short time, has good predictive accuracy regardless of surgical discipline.

2. Introduction and aims with references

Postoperative delirium (POD) is an often-unrecognized postoperative adverse event in older adults (Inouye et al., 2014; Rieck et al., 2020; Ryan et al., 2013). Defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) and the 10th revision of the International Statistical Classification of Disease and Related Health Problems (ICD-10), delirium is an acute and fluctuating disturbance of awareness, attention and cognition caused by an organic pathophysiology (American Psychiatric Association, 2013; World Health Organization, 2015). POD is often divided into three different subtypes, based on the manifestation. It is distinguished between the hyperactive, the hypoactive and a mixed form of both. Especially, the hypoactive delirium often remains undetected in the average clinical setting because of its characteristics such as unawareness, decreased alertness and decreased motor activity (Meagher et al., 2012; Stransky et al., 2011; Yang et al., 2009).

2.1 Impact of POD

The incidence of POD varies in different surgical populations from 11 % to 51 % (Inouye et al., 2014). This wide range could be also explained by the different study designs (prospectively with testing or retrospectively using ICD coding). The high incidence of POD in association with the aging society poses a major challenge to the health care system, not only in Germany. The older generation will continue to grow steadily in the coming years. In 2050, the number of people aged 60 years and older will nearly have doubled. With increasing age, people suffer more frequently from disorders and often from several diseases at the same time (World Health Organization, 2017). Based on these facts, in future, the older and thus sicker generation will be the increased patient clientele in hospitals who will be at increased risk for developing POD.

POD is not only itself an adverse outcome, but it is also frequently described as a cause of broader complications, like increased postoperative morbidity and mortality as well as long-term cognitive impairment (Inouye et al., 2014; Marcantonio, 2017). Moreover, the effects of POD on the length of stay (LOS) in hospital and in intensive care unit (ICU) are often reported (Aziz et al., 2018; Hewitt

et al., 2019; Salluh et al., 2020; Robinson et al., 2009). Prolonged LOS may put older patients at increased risk for further complications, which may adversely affect their independence in life (National Health Services Improvement, 2018). Furthermore, POD not only carries far-reaching complications for each patient, but also negatively impacts hospital organizational resources (Gleason et al., 2014; Mc Donnell and Timmins, 2012; Weinrebe et al., 2016).

Besides organizational resources, the human resources for high quality care of older adults are also limited. It is commonly known that there is a shortage of nurses and physicians in hospital. Essentially, this means that a prolonged LOS associated with a POD overstretches these limited resources and makes it even more difficult to adequately care for older affected individuals (European Hospital and Healthcare Federation, 2018).

2.2 Risk factors and Screening

Numerous risk factors for the development of POD are described in the literature. Besides predisposing factors of the patient such as age, comorbidities, cognitive and functional impairments, there are also treatment-related precipitating factors (Aldecoa et al., 2017; Lindroth et al., 2018). These include, among others, the type of surgery and the length of ventilation and intensive care stay. In addition, external stressors or medications are also triggering factors for the development of POD (Aldecoa et al., 2017; Marcantonio E., 2017).

Based on the knowledge of certain risk factors, various delirium risk scores have been developed in the past. Additional to routine data, various validated scores include elaborate cognitive testing, laboratory parameters and estimated intraoperative and postoperative variables (Lindroth et al., 2017). Among other reasons, due to the time-consuming nature of risk assessment with the previously validated scores and the non-routine availability of data, POD screening is not yet a standard in German hospitals. However, in an updated guideline, the European Society of Anaesthesiology and Intensive Care (ESAIC) recommends standardized risk assessment for POD in older adults and an appropriate peri-operative management (De Hert et al., 2018).

Most of the POD risk factors described cannot be prevented, neither the predisposing factors nor the need for a surgical intervention. However, conservative prevention programs are already in place to reduce the incidence of delirium in the hospital. One study-proven conservative intervention is the modified Hospital Elder Life Program (mHELP), which reduced the odds of POD by 56% and the LOS by two days (Chen et al., 2017).

2.3 Aim of the study analysis

The aim of the prospective observational monocentric study “PRe-Operative Prediction of postoperative DElirium by appropriate SCreening” (PROPDESC) was to develop and validate a pragmatic POD risk screening score based on routine preoperative data (Menzenbach et al., 2020; Menzenbach et al., 2022). It complied within the principles of the declaration of Helsinki and was approved by the local institutional Ethics Committee at the Medical Faculty of the Rheinische Friedrich-Wilhelms-University of Bonn. Written informed consent was obtained from each patient. Furthermore, it was registered in the German Registry for Clinical Studies under the following number: DRKS00015715.

One of the most important factors for the risk score development was a simple and time-short applicability in clinical routine. Based on the results of the PROPDESC score, clinicians should be able to preoperatively assess POD risk and initiate preventive measures depending on clinical resources. The long-term goal is to implement the PROPDESC risk score in hospitals to improve the quality of patient care and, through derivative prevention, to reduce POD complications and thus preserve the limited resources of the health care system.

By performing sub-analysis, additional consideration should be given to the medico economic impact of POD. The objective of the cardiac surgery subgroup analysis was to measure the relationship of coded delirium diagnosis (ICD-10) in comparison to the actual incidence of tested delirium (Kirfel et al., 2021). This examination aimed to provide a current-state representation of coding practices, respectively, sensitivity for the complication POD. Furthermore, these results were compared with the data of the “Institut für das Entgeltsystem im Krankenhaus gGmbH” (InEK) in order to check the comparability of the results across Germany.

In addition, a univariate comparison was made to determine whether patients with developed POD had a comparatively more severe hospital stay (by the German Patient Clinical Complexity Level (PCCL)) than the non-POD patients. As a further aim of this subgroup analysis, the independent influence of POD on LOS in hospital and in ICU was tested multivariate.
The purpose of an additional sub-analysis was to investigate the influence of POD on hospital and ICU length of stay for patients aged 70 years and older (Kirfel et al., 2022). Detailed risk adjustment (for age, surrogate parameters for multimorbidity and perioperative markers) was used to test the adverse impact of POD on patients and hospital resources in a multivariate analysis.

In order to use the results of this study and the sub-analyses in a target-oriented way in the future, a Germany-wide multicentre validation of the PROPDESC score is planned and the funding has already been approved by the “Deutsche Gesellschaft für Anästhesiologie und Intensivmedizin” (DGAI). Due to the multicentre design of the study and the easy and short application of the risk-screening tool, a long-term implementation of the PROPDESC score in the participating centres would be highly desirable.

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3. Publications

3.1 Publication 1: PRe-Operative Prediction of postoperative DElirium by appropriate SCreening (PROPDESC) development and validation of a pragmatic POD risk screening score based on routine preoperative data

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Original Contribution

PRe-Operative Prediction of postoperative DElirium by appropriate SCreening (PROPDESC) development and validation of a pragmatic POD risk screening score based on routine preoperative data

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ABSTRACT

Study objective: To develop and validate a pragmatic risk screening score for postoperative delirium (POD) based on routine preoperative data.
Design: Prospective observational monocentric trial.
Setting: Preoperative data and POD assessment were collected from cardiac and non-cardiac surgical patients at a German university hospital. Data-driven modelling approaches (step-wise vs. component-wise gradient boosting on complete and restricted predictor set) were compared to predictor selection by experts (investigators vs. external Delphi survey).
Patients: Inpatients (≥60 years) scheduled for elective surgery lasting more than 60 min.
Measurements: POD was assessed daily during first five postoperative or post-sedation days with confusion assessment method for intensive and standard care unit (CAM-ICU/CAM), 4 'A's test (4AT) and Delirium Observation Screening (DOS) scale.
Main results: From 1023 enrolled patients, 978 completed observations were separated in development ($n = 600$; POD incidence 22.2%) and validation ($n = 378$; POD incidence 25.7%) cohorts. Data-driven approaches generated models containing laboratory values, surgical discipline and several items on cognitive and quality of life assessment, which are time consuming to collect. Boosting on complete predictor set yielded the highest bootstrapped prediction accuracy (AUC 0.767) by selecting 12 predictors, with substantial dependence on cardiac surgery. Investigators selected via univariate comparison age, ASA and NYHA classification, surgical risk as well as 'serial subtraction' and 'sentence repetition' of the Montreal Cognitive Assessment (MoCA) to enable rapid collection of their risk score for preoperative screening. This investigator model provided slightly lower bootstrapped prediction accuracy (AUC 0.746) but proved to have robust results on validation cohort (AUC 0.725) irrespective of surgical discipline. Simplification of the investigator model by scaling and rounding of regression coefficients into the PROPDESC score achieved a comparable precision on the validation cohort (AUC 0.729).
Conclusions: The PROPDESC score showed promising performance on a separate validation cohort in predicting POD based on routine preoperative data. Suitability for universal screening needs to be shown in a large external validation.

1. Introduction

Postoperative delirium (POD) is the most common complication of older patients [1] aged 60 years and older, [2] occurring frequently within the first five days after surgery. [3–5] Incidences of POD range from 15 to 50% [6] and may increase up to 75% with prolonged ventilation during intensive care treatment. [7] Although appearing as a transient, early, postoperative complication with acute fluctuating

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disorders of consciousness, attention, perception and cognitive abilities., [8,9] POD may have lasting adverse effects on long-term outcome such as increased postoperative morbidity and mortality, prolonged hospital stay with higher treatment effort or persistent care dependency and cognitive decline. [1,10,11] With an estimated worldwide 2-fold increase of people over 65 by 2050 [12] and concurrently growing volume of surgical procedures, [13] POD is becoming an increasing challenge for healthcare systems.

Risk for POD is assumed to be determined by both patient-related predisposing factors and treatment-associated precipitating factors. Cognitive, sensory and functional impairments, multi-morbidity, polypharmacy and frailty are considered to be predisposing factors frequently related to ageing. [14] The resulting vulnerability is met by a second hit from precipitating factors such as surgery, pain, inflammation, exacerbation of chronic diseases and other external stressors or medication as triggers for POD. [1] Multifactorial pathogenesis of POD requires bundles of measures for prevention. Applying a modified Hospital Elder Life Program (mHELP), Chen et al. achieved a 56% reduction of POD within the intervention group versus control participants. [15] Considering limited resources of healthcare, these personnel- and cost-intensive efforts may have to be directed only at patients at increased risk. In order to focus prevention on patients at risk, routine screening for POD risk prior to surgery is essential and recommended by guidelines on postoperative delirium. [14,16]

In recent decades, several attempts have been made to build prognostic delirium risk models. Thus far, externally validated models [17] require extensive cognitive testing, functional assessments or laboratory values, and partly include further scores or data not available regularly prior to surgery. The resulting time consumption and preoperative lack of information hinder their implementation into clinical routine of surgical patients. Preoperative POD risk screening of older patients requires consistent applicability based on regularly available information. Thereby, a model composition of easy to asses variables supports universal use. [17] Moreover, adequate statistical processing [18,19] and standardised reporting on performance [20] in model development is demanded. To address this, model building requires both statistical and clinical input.

Aim of PROPDESC was to generate a universal pragmatic score based on preoperative data from patients of various surgical disciplines, which is easily applicable and thus can be implemented in clinical routine for preoperative POD risk screening. The PROPDESC score is intended to guide decision-making on preoperative POD-prevention in clinical application and to support further research on POD-management in scheduled trials.

2. Methods

2.1. Study design

PROPDESC is an investigator-initiated prospective monocentric observational trial conducted by the Department of Anesthesiology and Intensive Care Medicine at the University Hospital Bonn after approval by the Ethics Commission of the Medical Faculty of the Rheinische Friedrich-Wilhelms-Universität Bonn, Germany (application number 255/17). Participants were included after written informed consent during preoperative evaluation between 3rd September 2018 and 2nd October 2019. Preoperative data recording and patient testing were conducted in the anesthesia outpatient department and in the standard care wards. Postoperative assessment was performed in the intensive care and standard care units. Structured data and test results were entered pseudonymized (person-identifying data have been replaced by identification number) into an electronic database (REDCap), which was administered by the Institute for Medical Biometry, Informatics and Epidemiology at the University of Bonn.

In accordance with the study protocol, [21] 1097 patients were continuously included in PROPDESC. The first 600 patients with completed POD assessment constituted the development cohort to fit the risk model. Subsequent patients served as separate validation cohort to fairly evaluate its predictive performance. The definition of completed POD assessment required a valid conduct of at least three of the five scheduled postoperative visits to assess POD as primary outcome. Discharge to home before a third visit was accepted as exception to this rule, on the assumption that patients would not subsequently become delirious in their familiar environment. Therefore, these patients were rated as non-delirious unless they received a positive delirium diagnosis before their discharge. Patients who died during the 5-day visit period were rated as delirious if they presented POD prior to death. If they died without manifesting POD before completion of visit period, they were excluded from the analysis because it could not be ruled out that they could have developed POD during the study period.

2.2. Participants

Inpatients admitted to the Department of Anesthesiology for preoperative evaluation from cardiac and different non-cardiac surgical disciplines (orthopedics, thoracic, abdominal, vascular and others such as head, neck or mammary surgery) of the University Hospital Bonn were enrolled. Patients 60 years and older scheduled for elective surgery lasting more than 60 min were eligible (Inclusion criteria). Exclusion criteria were emergency procedures, language barriers and pre-existing mental retardation or severe dementia as determined by the physician, which constitute a lack of compliance to the study protocol by inhibiting adequate cognitive testing, delirium assessment and preclude contractual capacity to consent. [21]

2.3. Outcome

A positive POD diagnosis was considered if any of the applied assessment methods, specified below, detected POD at least once during the 5-day visit period. Delirium assessments were conducted every morning by trained study personnel on each of the first five days after surgery, or the first five days after the end of sedation. Sedated patients with Richmond Agitation-Sedation Scale (RASS) [22] score < -3 were considered as not assessable and therefore their testing for POD was initiated after exceeding this level of sedation according to CAM-ICU. [7,23] Application of various validated test instruments for POD assessment was distinguished for intensive care and standard care units. Confusion Assessment Method for ICU (CAM-ICU) was used for intensive care patients. Confusion Assessment Method (CAM) [24] and 4 'A's Test (4AT) [25] incorporating Alertness, Abbreviated Mental Test-4, Attention (Month Backwards test) and Acute change and fluctuating course were conducted on patients in standard wards. In order not to miss the diagnosis of delirium due to spot examination based on once-daily rounds by the study staff, the nurse in charge was queried at each visit about behavioural problems in the previous 24 h by using the 13-item Delirium Observation Screening Scale (DOS) [26] in addition to the above mentioned assessments. POD diagnosis was rated positive from a 4AT of 4 points or a DOS of 3 onwards. For each of the applied instruments, there is a risk of a type 1 error (false positive). Nevertheless, due to the known high number of undetected POD in clinical practice, this was judged to be less relevant than the risk of missing a POD diagnosis in terms of a type 2 error (false negative). Accuracy of POD assessment was promoted by extensive training of study staff and regular supervision by experienced physicians with expertise on POD for internal monitoring purposes. Study team members were instructed and trained in test administration prior to the start of the study. At the beginning of the study, a daily debriefing was conducted to clarify any questions that may have arisen during test performance. During the ongoing process of study implementation, a routine meeting with the study team was held once a month to discuss the progress of the study. Questions arising at short notice were clarified directly on site. Inclusion and assessment of patients for the validation cohort were conducted

continuously in the same manner as for the development cohort without information on statistical analysis in order to reduce detection bias.

2.4. Predictors

Preoperative data assessed by physicians of the Department of Anesthesiology during preoperative evaluation were collected and supplemented with cognitive testing and additional specific medical history by study personnel. Baseline characteristics included age, sex, body mass index (BMI), American Society of Anesthesiologists (ASA) Physical Status Classification System, Revised Cardiac Risk Index (rCRI), New York Heart Association Classification (NYHA), Metabolic Equivalent of Tasks (MET), surgical risk, surgical discipline, long-term medication, and preoperative laboratory values. To asses surgical risk the 5-level Johns-Hopkins classification [27] of intervention risk commonly used in the department was transformed into 3-level modified Johns Hopkins surgical criteria [28] similar to 3-level classification according to ESAIC guidelines [29,30] (adapted from Glance et al. [31]) for study purposes. In this process, 5-level Hopkins classes 1 and 2 were assigned to low-risk surgery, class 3 to intermediate-risk surgery, and classes 4 and 5 to high-risk surgery. [32]

In addition, study personnel performed the Montreal Cognitive Assessment (MoCA) [33] to detect pre-existing cognitive impairment. Subjective quality of life and physical function were assessed by the EQ-5D-5L and EQ-VAS [34,35]. Furthermore, preoperative assessable items of Kim's DELirium Prediction based on Hospital Information (DELPHI) score [36] were collected.

2.5. Sample size

Under the assumption of a POD incidence of about 30% in a mixed cohort of the university hospital and a required number of 10–20 events per variable (EPV) [37,38] to be estimated by a logistic regression model, the size of the development cohort was set to 600 patients. In order to obtain a reasonable number of events for the separate validation cohort, the planned sample size was set to at least 1000 patients.

2.6. Missing data

Frequencies of missing values are reported for all considered predictor variables and the outcome. For the bootstrap validation on the development cohort, we considered a complete case analysis to evaluate all considered models with the same sample size. For fitting the final model, only observations that had a missing value in one of the selected variables were excluded.

2.7. Statistical analysis methods

Statistical analysis was performed using the statistical programming environment R. For the description of the cohorts, continuous and ordinal variables are presented with mean and ± standard deviation (sd). Nominal variables are reported as numbers and percentages. Laboratory values are presented with median and inter-quartile range (IQR), due to the inherent skewness. Differences between the development and the validation cohort were analysed using the non-parametric Wilcoxon rank-sum test for continuous variables, and Fisher's exact test for categorical variables, considering a two-sided significance level of 0.05. For the first assessment of predictors, univariate logistic regression models were fitted with POD as outcome and the corresponding predictors as only explanatory variable. Odds-ratios from these models are reported, together with 95% confidence intervals (CI) and Likelihood-Ratio tests.

Different data-driven and subject-matter specific model building procedures were performed for risk score development. The resulting models were internally validated on the development cohort via bootstrapping (drawing 1000 bootstrap samples), therefore avoiding overoptimistic results like in classical internal validation. All modelling decisions were based solely on the performance in the bootstrap analysis. Afterwards, the finally selected model was estimated on the complete development cohort and subsequently evaluated on the separate validation cohort. Due to the non-random splitting of the data in development and validation cohort, this procedure can be considered as similar to an external validation. [39]

As evaluation criteria both in the bootstrap analysis on the development cohort and the quasi-external validation [39] on the validation cohort we considered the AUC (equivalent to the c-statistic) for the discriminatory power of the resulting models as well as the Brier Score (which additionally takes calibration into account).

After the final selection and estimation of the prediction model and its evaluation on the validation set, we additionally adapted the model to a simplified risk score via scaling and rounding of regression coefficients to the nearest integer. Subsequently, this simplified score was also validated on the validation cohort and its results are reported alongside the complete prediction model.

2.8. Model-building procedures

The study design included the collection of an extensive data set containing a large array of tests to explore and evaluate potential predictors to generate prognostic models. In collaboration between statisticians with expertise in statistical learning algorithms and experienced clinicians of investigators to provide clinical input, different prognostic models have been developed and analysed. In the comparison of different models the maximum achievable predictive accuracy of a comprehensive model was intended to be balanced against the applicability of a simplified risk score for clinical routine.

2.8.1. Step-wise model and boosting model

As purely data-driven model-building procedures we considered both a classical automated step-wise backward predictor selection (with the AIC criterion) [40,41] as well as a statistical learning algorithm (component-wise gradient boosting) [42] in combination with logistic regression. In both approaches, POD served as outcome, while all available predictors were considered as potential explanatory variables. The boosting approach originates from machine-learning and performs automated variable selection and regularization via gradient descent in function space in combination with early stopping. [43] As base-learners, we considered linear regression models for all continuous and categorical predictors. Tuning of the boosting algorithm was performed using 25-fold bootstrap on the considered training data. [44]

2.8.2. Restrictive boosting model

Since the aim of PROPDESC was to provide a feasible tool for POD prediction in clinical routine, an additional model was fitted on a restricted set of predictors containing only preoperative regularly available or easily obtainable parameters. For this purpose, laboratory values and the sum of MoCA test were excluded and the boosting approach was again performed on the restricted set of base-learners.

2.8.3. Investigator model

As a subject-matter strategy, investigators of PROPDESC selected predictive and easily obtainable parameters based on univariate comparisons in the development cohort and their assessment of feasibility to compose an investigator risk model for simple application in clinical practice.

2.8.4. Delphi survey model

Aspiring a more objective level of expert judgement on feasibility, to create a generally applicable and commonly adopted risk score, a Delphi expert survey was conducted to select variables collected by PROPDESC with regard to their expected prediction ability and feasibility in everyday practice. A panel of seventeen experienced clinicians from

several German hospitals with expertise on POD (as listed in acknowledgements) completed a two-stage Delphi survey as external experts without having information on descriptive and outcome statistics such as univariate logistic regression of the investigated PROPESC collective. In the first round, favoured parameters of the complete preoperative data set should be preselected by yes-no voting. The results of the first round were reported to the panel as reference for the second round. Based on this, parameters preselected by the first round were scored in terms of expected predictivity and feasibility in clinical practice using a five-level Likert scale. Additionally, a recommendation regarding the number of parameters included in their (Delphi survey) model was asked for.

3. Results

3.1. Participants

1097 eligible patients consented to participate in this observational study. The flow chart (Fig. 1) shows the case number of participants and their exclusion criteria. 72 patients did not undergo surgery for various reasons during the observation period. Another two patients withdrew their consent and were also considered as study dropouts. Of the remaining 1023 enrolled patients, 15 died during the 5-day visit period without manifesting POD. Since the completion of assessment for the primary endpoint of POD was not possible, these patients were also removed from the cohort. Additional 30 patients had less than three completed visits at the end of the study without having exhibited POD and were removed. However, patients who were discharged prior to a visit on the third day without manifesting POD before, were included as non-delirious on the assumption that they would not subsequently become delirious in their family environment. With this approach, 978 patients were included in the analysis.

The overall POD rate was 23.5% ($n = 230$). Baseline characteristics of the study collective are presented in Table 1. The total population had a mean age of 72.3 ± 7.3 years (38.3% women and 61.6% men). There were no significant differences in patient characteristics between the development and validation cohort.

Delirium incidence in the development cohort was 22.2% ($n = 133$) and 25.7% ($n = 97$) in the validation cohort. The highest incidence of delirium was observed after cardiac surgery procedures, with 52.0% in the development cohort. Table 2 shows the preoperatively collected variables for the non-POD and POD group of the development cohort. The delirious patients had a higher amount of continuous medication. Furthermore, the delirious patients had a higher mean troponin value and NT pro-BNP value preoperatively. On average delirious patients performed worse in risk assessments such as ASA, NYHA, rCRI, MET. In preoperative MoCA, delirious patients performed substantially lower than the non-delirious patients. Likewise, the delirious patients showed a lower Delphi [36] sum score. In terms of quality of life, non-delirious patients reported a higher score preoperatively.

Table 1
Patient characteristics in relation to the development and validation cohort.

Characteristics	Total (n = 978)	Development cohort (n = 600)	Validation cohort (n = 378)	P value
Age (mean, sd)	72.3 ± 7.3	72.5 ± 7.2	71.9 ± 7.4	0.189
Sex				0.840
Female	375 (38.3)	232 (38.7)	143 (37.8)	
Male	602 (61.6)	368 (61.3)	234 (61.9)	
BMI (mean, sd)	27.7 ± 5.4	27.9 ± 5.6	27.4 ± 5.2	0.184
No. of medication (mean, sd)	6.0 ± 3.5	6.1 ± 3.5	5.7 ± 3.3	0.151
ASA				0.147
ASA 1	25 (2.6)	16 (2.7)	9 (2.4)	
ASA 2	339 (34.6)	224 (37.3)	115 (30.4)	
ASA 3	545 (55.7)	318 (53.0)	227 (60.1)	
ASA 4	69 (7.1)	42 (7.0)	27 (7.1)	
NYHA				0.917
NYHA I	413 (42.2)	252 (42.0)	161 (42.6)	
NYHA II	336 (34.4)	206 (34.3)	130 (34.4)	
NYHA III	212 (21.7)	130 (21.7)	82 (21.7)	
NYHA IV	17 (1.7)	12 (2.0)	5 (1.3)	
rCRI				0.531
rCRI 1	409 (41.8)	257 (42.8)	152 (40.2)	
rCRI 2	243 (24.9)	142 (23.7)	101 (26.7)	
rCRI 3	219 (22.4)	139 (23.2)	80 (21.2)	
rCRI 4	107 (10.9)	62 (10.3)	45 (11.9)	
MET				0.722
MET <1	11 (1.1)	5 (0.8)	6 (1.6)	
MET 1–4	459 (46.9)	284 (47.3)	175 (46.3)	
MET 5–10	475 (48.6)	290 (48.3)	185 (48.9)	
MET >10	33 (3.4)	21 (3.5)	12 (3.2)	

Data are number (%) unless stated otherwise. IQR = interquartile range, BMI = body mass index, ASA = American Society of Anesthesiology, NYHA = New York Heart Association, rCRI = Revised Cardiac Risk Index, MET = Metabolic Equivalent of Tasks. *P*-values refer to Wilcoxon tests for continuous variables and Fisher tests for categorical ones.

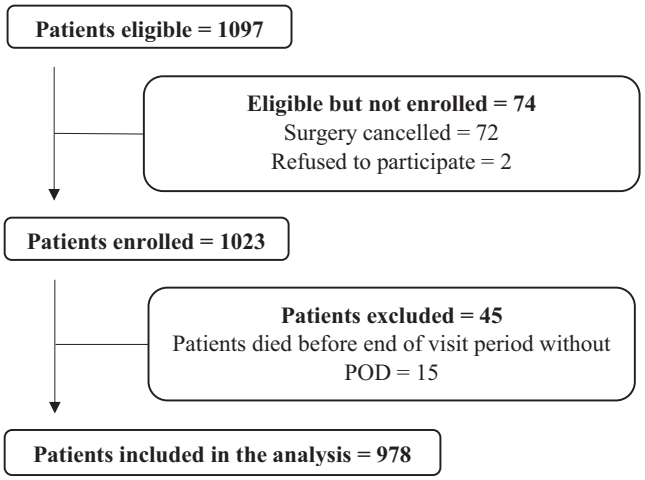

Fig. 1. Flow chart of patients in the PROPDESC cohort.

3.2. Model development and internal validation via bootstrapping

In the bootstrap analysis, the boosting approach selected prediction models containing on average 11 predictor effects (continuous variables or categorical effects) yielding a median AUC of 0.767 (Brier-Score: 0.142), while the classical step-wise procedure selected on average 8 variables yielding a median AUC of 0.737 and a Brier score of 0.152. Boosting on restricted predictor set (restricted boosting model) yielded a median AUC of 0.756 (Brier score of 0.144) and contained on average 16 predictor effects.

Selection of a variable set by investigators after univariate regression for a feasible clinical application resulted in a model compilation of age, ASA, NYHA, surgical risk, serial subtraction task (according MoCA on attention with maximum 3 points achievable) and repetition of two

Table 2
Predictors for POD for the development cohort, non-POD and POD group.

Predictors	Development cohort (n = 600)		P value	OR	CI (95%)	Missing data
	Non-POD	POD				
No.	467 (77.8)	133 (22.2)				
Age (mean, sd)	72.1 ± 7.2	73.8 ± 7.3	0.019	1.0	1.0–1.1	0 (0.0)
Sex			0.020			0 (0.0)
Female	192 (41.1)	40 (30.1)		Ref. = 1.0		
Male	275 (58.9)	93 (69.9)		1.6	1.1–2.5	
BMI (mean, sd)	28.1 ± 5.6	27.5 ± 5.3	0.303	1.0	0.9–1.0	2 (0.3)
No. of medication (mean, sd)	5.9 ± 3.6	6.7 ± 3.3	0.019	1.1	1.0–1.1	38 (6.3)
ASA			<0.001			0 (0.0)
ASA 1	15 (3.2)	1 (0.8)		Ref. = 1.0		
ASA 2	205 (43.9)	19 (14.3)		1.4	0.2–61.6	
ASA 3	223 (47.8)	95 (71.4)		6.4	1.0–271.5	
ASA 4	24 (5.1)	18 (13.5)		11.3	1.4–498.1	
NYHA			<0.001			0 (0.0)
NYHA I	223 (47.8)	29 (21.8)		Ref. = 1.0		
NYHA II	158 (33.8)	48 (36.1)		2.3	1.4–4.0	
NYHA III	79 (16.9)	51 (38.4)		5.0	2.9–8.7	
NYHA IV	7 (1.5)	5 (3.8)		5.5	1.3–21.4	
rCRI			<0.001			0 (0.0)
rCRI 1	232 (49.7)	25 (18.8)		Ref. = 1.0		
rCRI 2	113 (24.2)	29 (21.8)		2.4	1.3–4.4	
rCRI 3	86 (18.4)	53 (39.9)		5.7	3.2–10.2	
rCRI 4	36 (7.7)	26 (19.6)		6.7	3.3–13.5	
MET			0.002			0 (0.0)
MET <1	3 (0.6)	2 (1.5)		Ref. = 1.0		
MET 1–4	203 (43.5)	81 (60.9)		0.6	0.1–7.3	
MET 5–10	244 (52.3)	46 (34.6)		0.3	0.0–3.5	
MET >10	17 (3.6)	4 (3.0)		0.4	0.0–5.8	
Surgical discipline			<0.001			0 (0.0)
Others	112 (24.0)	13 (9.8)		Ref. = 1.0		
Cardiac surgery	73 (15.6)	79 (59.4)		9.3	4.7–19.5	
Orthopedics	192 (41.1)	28 (21.1)		1.3	0.6–2.8	
Thoracic surgery	8 (1.7)	2 (1.5)		2.2	0.2–12.5	
Abdominal surgery	70 (15.0)	7 (5.3)		0.9	0.3–2.5	
Vascular surgery	12 (2.6)	4 (3.0)		2.9	0.6–11.4	
Surgical risk			<0.001			0 (0.0)
Low	94 (20.1)	3 (2.3)		Ref. = 1.0		
Intermediate	234 (50.1)	46 (34.6)		6.2	1.9–31.6	
High	139 (29.8)	84 (63.2)		18.9	5.9–95.9	
Laboratory (median, (IQR))						
Haemoglobin (in g/dl)	13.6 (2.3)	13.3 (2.5)	0.124	0.9	0.8–1.0	0 (0.0)
Haematocrit (in %)	39 (7)	39 (7)	0.083	1.0	0.9–1.0	0 (0.0)
HbA1c (in %)	5.7 (0.7)	5.8 (0.9)	0.003	1.4	1.1–1.7	4 (0.7)
Leucocyte count (in G/l)	7.4 (2.6)	7.3 (2.4)	0.440	1.0	0.9–1.0	0 (0.0)
Sodium (in mmol/l)	140 (4)	140 (3)	0.885	1.0	0.9–1.1	0 (0.0)
Potassium (in mmol/l)	4.5 (0.5)	4.3 (0.5)	0.010	0.6	0.4–0.9	0 (0.0)
Creatinine (in mg/dl)	0.9 (0.3)	0.9 (0.4)	0.340	1.1	0.9–1.5	0 (0.0)
Total protein (in g/l)	69.4 (5.9)	69.5 (8.2)	0.137	1.0	0.9–1.0	5 (0.8)
C-reactive protein (in mg/l)	3.1 (6.9)	2.7 (7.3)	0.157	1.0	1.0–1.0	2 (0.3)
Troponin T (in ng/l)	10.8 (11.9)	16.2 (19.0)	<0.001	1.0	1.0–1.0	0 (0.0)
NT pro-BNP (in pg/ml)	165.0 (363.8)	367.5 (849.3)	0.052	1.0	1.0–1.0	21 (3.5)
Validated scores (mean, sd)						
Delphi Score sum	4.3 ± 2.1	6.1 ± 1.6	<0.001	1.6	1.4–1.8	0 (0.0)
EQ-5D-5L						
Mobility	2.4 ± 1.4	2.1 ± 1.4	0.063	0.9	0.8–1.0	0 (0.0)
Self-care	1.5 ± 0.9	1.4 ± 1.0	0.902	1.0	0.8.1.2	1 (0.2)
Usual activities	2.0 ± 1.3	1.9 ± 1.3	0.385	0.9	0.8–1.1	0 (0.0)
Pain/discomfort	2.6 ± 1.3	2.2 ± 1.2	0.002	0.8	0.7–0.9	0 (0.0)
Anxiety/depression	1.7 ± 1.0	1.7 ± 1.1	0.498	1.1	0.9–1.3	2 (0.3)
EQ-VAS	61.6 ± 22.2	58.8 ± 23.3	0.218	1.0	1.0–1.0	3 (0.5)
MoCA sum	23.3 ± 3.8	21.8 ± 4.2	<0.001	0.9	0.9–1.0	0 (0.0)
Trail making test	0.6 ± 0.5	0.5 ± 0.5	0.021	0.6	0.4–0.9	4 (0.7)
Copy cube	0.5 ± 0.5	0.4 ± 0.5	0.398	0.8	0.6–1.2	4 (0.7)
Clock drawing	2.4 ± 0.8	2.3 ± 0.9	0.064	0.8	0.6–1.0	4 (0.7)
Naming animals	2.9 ± 0.3	3.0 ± 0.2	0.157	1.8	0.8–4.9	2 (0.3)
Repeating numbers	1.7 ± 0.6	1.5 ± 0.6	0.051	0.7	0.5–1.0	0 (0.0)
Letter attention	0.9 ± 0.3	0.8 ± 0.4	0.121	0.7	0.4–1.1	0 (0.0)
Subtraction	2.8 ± 0.6	2.6 ± 0.8	0.008	0.7	0.5–0.9	0 (0.0)
Sentence repetition	1.5 ± 0.7	1.3 ± 0.8	0.017	0.7	0.6–0.9	1 (0.2)
Fluency language	0.4 ± 0.5	0.3 ± 0.4	0.020	0.6	0.4–0.9	1 (0.2)
Abstraction	1.1 ± 0.8	1.0 ± 0.8	0.395	0.9	0.7–1.1	0 (0.0)
Memory	2.4 ± 1.6	1.8 ± 1.6	<0.001	0.8	0.7–0.9	0 (0.0)
Orientation	5.9 ± 0.6	5.8 ± 0.6	0.234	0.8	0.6–1.1	0 (0.0)
Education level	0.4 ± 0.5	0.5 ± 0.5	0.138	1.3	0.9–2.0	1 (0.2)

Data are number (%) unless stated otherwise. IQR = interquartile range, POD=Postoperative delirium, OR = Odds Ratio, CI=Confidence Interval, Ref. = Reference, BMI = body mass index, ASA = American Society of Anesthesiology, NYHA = New York Heart Association, rCRI = Revised Cardiac Risk Index, MET = Metabolic Equivalent of Tasks, MoCA = Montreal Cognitive Assessment. p-values refer to Likelihood-Ratio test on univariate logistic regression models with POD as outcome and the corresponding predictor as only explanatory variable.

syntactically complex sentences (according MoCA on language with maximum 2 points achievable). This investigator model achieved a slightly lower bootstrapped median AUC of 0.746 (Brier-Score: 0.150).

As consensus of the Delphi survey among external experts, without having information on descriptive or statistical data of the PROPDESC collective, an average model size of seven parameters was preferred. In total, 16 variables (listed in Supplementary Table 1) received at least 60% agreement in the first survey round. Their rating results for predictivity and feasibility by a five-level Likert scale in the second survey round are also shown in Supplementary Fig 1 of the supplements. The seven best rated variables were compiled into a model. This Delphi survey model achieved a median AUC of 0.582 (Brier-Score of 0.170) in the internal bootstrap analysis.

An overview on the different considered prediction models and their coefficients from logistic regression, fitted on the complete development cohort, is displayed in Supplementary Table 2 of the supplements.

3.3. Model specification

The different AUC and Brier scores from internal bootstrap validation show that the boosting model is estimated to perform best in terms of POD prediction (Table 3). Nevertheless, due to the expected better applicability in clinical routine with easy to collect variables and low time consumption, the investigator model was chosen as the final model accepting a moderate decrease in AUC and a slightly higher Brier score. Since the PROPDESC risk score is not only intended to be applicable in university hospitals with cardiac surgery, internal validation was also performed for the subgroup without cardiac surgery. The AUC drops slightly when excluding patients with cardiac surgery. This decrease in AUC with respect to non-cardiac patients was the smallest for the investigator model compared to the other models (Table 3).

3.4. Final model and performance on validation cohort

The final model (investigator model) yielded an AUC of 0.725 (Brier score = 0.172) on the validation cohort (Table 3, Fig. 2), therefore showing a slightly lower performance on a completely separate cohort compared to the internal bootstrap validation. The coefficients for the final model are presented in Table 4. Predicted probabilities for individual patients can be computed by:

$$1/(1+exp(-(\,7.8168+0.0456\,Age\;[years]+0.4619\,ASA\;[points]+0.3842\,NYHA\;[points]+1.8894\;[if\;surgery\;risk\;is\;intermediate]$$
$$+2.7734\;[if\;surgical\;risk\;is\;high]-0.2731\,MoCA\;repetition\;of\;sentences-0.2376\,MoCA\;serial\;subtracing\;)\,)\,).$$

The simplified "bedside" risk score is calculated by summing up 1 point per year, 10 points each per class of ASA and NYHA, 40 points for intermediate or 60 points for high surgical risk and finally subtracting 5 points for each point achieved on MoCA items (Table 4). The simplified score showed a very similar performance (AUC = 0.729, Fig. 2) on the validation cohort. The corresponding probabilities for a new patient regarding different score levels can also be derived from Table 4. The performances on a subsample without cardiac surgery were nearly identical with an AUC = 0.724 for the complete prediction model and AUC = 0.722 for the simplified score.

4. Discussion

4.1. Principle findings

We developed and validated a prognostic model for POD based on a comprehensive preoperative dataset. The PROPDESC score estimates POD risk based on age, ASA physical status, NYHA classification, operative risk and short cognitive assessment (serial subtraction task and repetition of two syntactically complex sentences) according to MoCA on attention and language. Important features of the instrument are rapid and ready preoperative availability of required parameters as recommended by guidelines on postoperative delirium. [14]

4.2. Strengths and weaknesses of the study

The final PROPDESC model was composed aiming for feasibility by investigators based on univariate comparisons in the development cohort. The investigator model compiled in this way (containing 6 variables) performed just slightly below purely data-driven statistical learning procedures with respect to prediction accuracy via bootstrapping on development cohort (median $AUC_{investigator}$ of 0.746 vs. median $AUC_{boosting}$ of 0.767). Boosting approaches provided models with the highest prediction accuracy, but consisted of more variables (12 to 16) and, in particular, contained more cognitive tests or patient surveys which have to be collected additionally to routine. Furthermore, PROPDESC included a notable proportion of cardiac surgery patients with a POD incidence considerably above average of total collective. Thus cardiac surgery contributed substantially to prognostic power in purely data-based models. The predictive power of the investigator

Table 3
Results from the bootstrap analysis on the development cohort for all considered prediction models as well as the results on the validation cohort for the final prediction model (investigator model) and the simplified score. The Brier score can only be computed for the probabilistic models, and not the simplified score. For sensitivity reasons, validation was also performed on a cohort without cardiac surgeries (AUC non-cardiac).

Bootstrap analysis on Development Cohort	*AUC (median)*	*Range (min–max)*	*Brier score (median)*	*Range (min–max)*	*AUC non-cardiac surgery (median)*	*Range (min–max)*
Boosting model	0.767	0.649–0.854	0.142	0.128–0.185	0.643	0.417–0.826
Restrictive boosting model	0.756	0.636–0.850	0.144	0.129–0.178	0.631	0.387–0.793
Step-wise model	0.737	0.563–0.843	0.153	0.121–0.196	0.620	0.425–0.798
Delphi survey model	0.581	0.408–0.715	0.170	0.160–0.197	0.598	0.440–0.774
Investigator model	0.746	0.633–0.855	0.150	0.131–0.179	0.661	0.393–0.846
Validation cohort	*AUC*	*95% CI*	*Brier score*	*95% CI*	*AUC non-cardiac surgery*	*95% CI*
Prediction model (Investigator model)	0.725	0.672–0.777	0.172	0.151–0.193	0.724	0.648–0.798
Simplified score	0.729	0.677–0.782	–	–	0.722	0.647–0.798

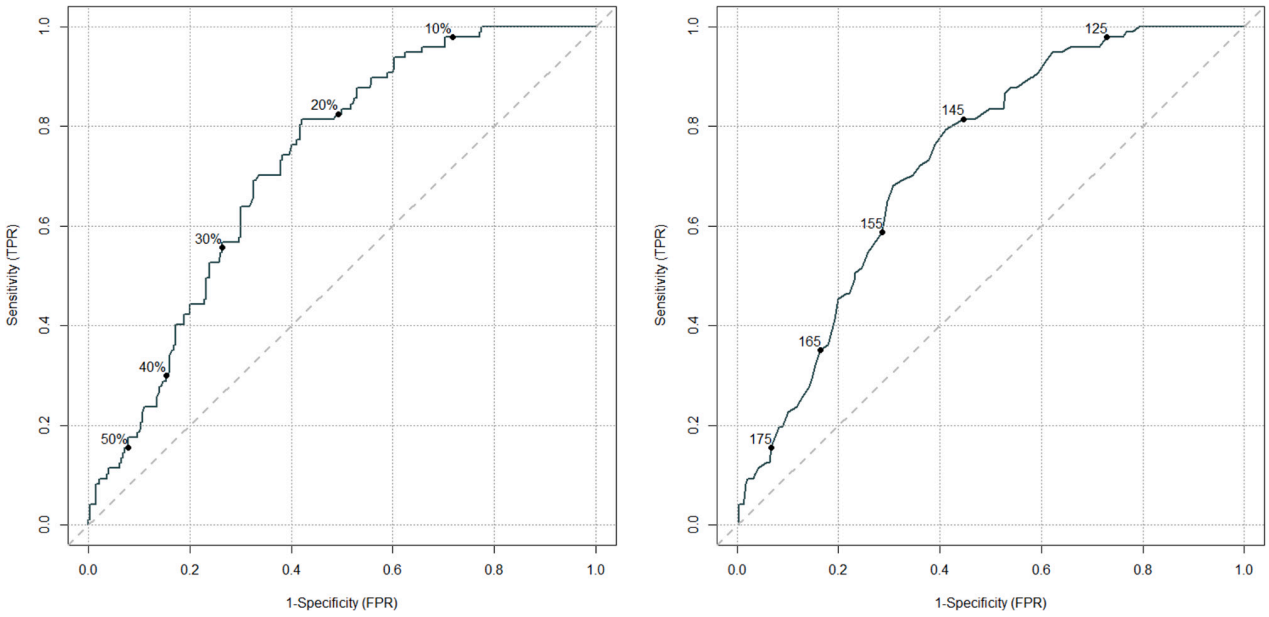

Fig. 2. Receiver-Operator-Characteristics (ROC) Curves for the final prediction model (left) and the simplified score (right) on validation cohort. Potential cutpoints for risk-stratification are displayed as individual percentages for final prediction model (left) and as total score points for simplified score (right).

Table 4
Coefficients for the final prediction model (investigator model) estimated via logistic regression on the development cohort and a simplified score (derived via scaling and rounding of coefficients).

Variables	Coefficients	Simplified score
Intercept	−7.8168	
Age	0.0465	Age (in years)
ASA Classification	0.4619	+ 10 * (result of ASA class)
NYHA Classification	0.3842	+ 10 * (result of NYHA class)
Surgical risk intermediate	1.8894	+ 40 [if surgical risk = intermediate]
Surgical risk high	2.7734	+ 60 [if surgical risk = high]
Serial subtracting (MoCA)	−0.2376	− 5 * (result of subtracting)
Repetition of two sentences (MoCA)	−0.2731	− 5 * (result of repetition of sentences)
Simplified score rating and corresponding POD risk	*Rating*	*POD risk*
	<125 points	<10%
	125–144 points	10–20%
	145–154 points	20–30%
	155–164 points	30–40%
	165–174 points	40–50%
	≥175 points	>50%

ASA = American Society of Anesthesiology, NYHA = New York Heart Association, MoCA = Montreal Cognitive Assessment, POD=Postoperative Delirium.

model proved robust on the separated validation cohort, irrespective of surgical discipline (AUC_{total} 0.725 vs. $AUC_{non\text{-}cardiac}$ 0.724). The simplified bed-side score of this investigator model showed a comparable AUC of 0.729 on that validation cohort.

4.3. Key principles for model development

Key principles for development of a prognostic model on POD risk include (1) to sample a sufficient number of patients, (2) to investigate a comprehensive data set of preoperative information addressing multifactorial genesis of POD and (3) to provide sensitive detection of primary endpoint, as missing POD diagnosis in clinical practice is likely high.

(1) Number of patients with positive POD diagnosis in the development cohort (n = 133) results in an EPV of 1:22 on 6-paramater PROPDESC score. Lindroth et al. demand just an EPV of at least 1:10 to avoid statistical overfitting, which could impair validation. [17]

(2) PROPDESC score accounts for risk components of different etiologies by factoring age, comorbidity, functional status, surgical invasiveness and cognitive performance.

(3) POD assessment was conducted on the first five days after surgery or end of sedation. This is considered the interval with highest probability of POD occurrence, according to the literature. Study staff performed daily examinations (including weekends) with validated instruments. These spot checks were supplemented by DOS survey of nursing staff to avoid missing POD.

4.4. Comparison to other studies

Despite the effort to compare several different modelling approaches including complex machine learning algorithms, the models in this study did not reach a comparably high predictive accuracy as the best model (AUC = 0.94) [36] reported in a meta-analysis. [17] However, Kim conducted enrolment partly after POD onset in his Delphi trial and also involved data not available prior to surgery for development of his prediction model. [36] Further models [17] provided a comparable AUC to PROPDESC score, but relied on information of extensive cognitive testing not applicable as preoperative routine.

Intending to develop a compact predictive model, Lindroth et al. developed a so-called two-factor model. [45] However, these factors are the NSQIP-SC score, which consists of 21 preoperative parameters including the Current Procedural Terminology (CPT) code out of 1557 unique codes in combination with the Trail making test B (TMTB). Since the NSQIP-SC is not automatically available pre-operatively in every country and the TMTB requires a paper sketch and the ability to draw, this construct does not seem to be suitable as rapid assessment for clinical routine and preoperative bedside screening. Furthermore, the achieved predictive accuracy with an AUC of 0.81 was determined in an analysis of only 97 patients. Enhancing the American College of Surgeons NSQIP Surgical Risk Calculator to predict the geriatric-specific outcomes “pressure ulcer, delirium, new mobility aid use, and

functional decline", it was supplemented by 6 additional parameters to the previous 21. Thus, it seems unsuitable for rapid patient-side application during preoperative evaluation as well. [46]

A recently published study [47] with a comparable number of cases to PROPDESC, was limited to abdominal surgery patients and also considered postoperative status as surgical APGAR (sAPGAR) [48] in addition to preoperative risk factors for POD prediction. Li et al., similarly to PROPDESC, did not include patients with pre-existing dementia, delirium, or disorders of consciousness in their trial. [47]

In order to screen a patient collective for POD risk, the entire sample should be evaluated for detecting patients at risk. A complex risk score with a slightly higher precision does not provide a better screening efficacy if it is not routinely applicable and thus many patients remain unassessed Aiming to develop a screening tool, we prioritised the simpler applicability of the investigator model over the highest accuracy of the boosting model, which is rather required for diagnostic tools. Predictive power and rapid assessment of the PROPDESC score is expected to enable decision making on POD prophylaxis in clinical routine. For example, despite an AUC_{mean} of 0.69, preoperative APFEL score for estimating the risk of postoperative nausea and vomiting (PONV) has proven useful for decision making on PONV prophylaxis because of simple handling in clinical practice. [49]

The PROPDESC score is intended for risk screening in clinical use and future research. If the score indicates an increased risk by the collected risk factors (age, ASA, NYHA, operative risk), cognitive testing (subtracting points for MoCA on attention and language, see Table 4) gains particular importance for decision-making in clinical practice. As model development and internal validation of PROPDESC were conducted in a monocentric setting, external multicentre validation is scheduled to confirm universal applicability.

4.5. Limitations

Limitations of the PROPDESC trial are the exclusion of patients with emergency procedures, language barriers and pre-existing mental retardation or severe dementia as determined by the physician. Consequently, on the one hand, these conditions were not considered as risk factors for POD when developing the score. On the other hand, they would have hindered adequate performance of pre- and postoperative cognitive assessments, as well as valid differentiation between pre-existing mental disorders and acute onset during POD.

The gold standard for diagnosing delirium would be an extensive examination by a psychiatrist, which however is usually not feasible in clinical routine of surgical patients. Therefore, POD assessment of this trial was also limited to the five-day assessment described above.

Another limitation to be mentioned is that although this study carefully separated development and validation cohort, one can still not rule out some overfitting and overoptimism in the validation as both cohorts were derived from the same hospital.

4.6. Conclusions

POD risk screening as recommended by guidelines on postoperative delirium [14] is intended to guide decision-making on preventive management in clinical practice. This study developed a risk score based on statistical and clinical input in a monocentric observational trial on older inpatients (≥60 years) from various surgical disciplines. The proposed PROPDESC score showed a good prediction accuracy irrespective of surgical discipline but requires only a short time to collect preoperative available parameters. This seems promising as universal risk screening tool, but demands subsequent external validation.

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Ethical approval

The work described has been carried out in accordance with the Declaration of Helsinki (Code of Ethics of the World Medical Association for experiments involving humans). Research ethics board approval was obtained by the Ethics Commission of the Medical Faculty of the Rheinische Friedrich-Wilhelms-Universität Bonn, Germany (Chairperson Prof K. Racké; application number 255/17).

Study design

The study protocol including amendments was finalized on 2nd of May 2018 as version 2.1. and has been published (org/10.1016/j.conctc.2019.100501). [21]

Study registration

This study was registered in the German Clinical Trials Register/ Deutsches Register Klinischer Studien (DRKS-ID: DRKS00015715).

Data sharing

The data generated and/or analysed during PROPDESC trial are available from the corresponding author on reasonable request.

Author contributions

Jan Menzenbach, Maria Wittmann and Vera Guttenthaler have substantially contributed to the interpretation of current specific knowledge, which resulted in the conception and design of the present trial. Jan Menzenbach, Andrea Kirfel, Andreas Mayr and Maria Wittmann are responsible for data clearing, for strategies of model development and for interpretation of results. Jan Menzenbach is sponsor and principle investigator of the present trial and participated in the acquisition of funding. Jan Menzenbach and Andrea Kirfel wrote the manuscript, revised it critically for important intellectual content, and approved the final manuscript. Vera Guttenthaler co-authored the manuscript.The study team consisted of physicians and non-physicians from the Clinic for Anesthesiology at the University Hospital of Bonn as well as doctoral students who were supervised by Maria Wittmann and Jan Menzenbach. PROPDESC Collaboration Group contributed to the data collection and external experts who participated in the Delphi survey are listed in the acknowledgements. Andrea Kirfel, Jan Menzenbach and Maria Wittmann are responsible for project management. Andreas Mayr and Christian Staerk wrote the statistical methods. Arcangelo Ricchiuto was responsible for the building, management and backup of the REDCap database. Statistical processing of the study data was supported and performed by the Institute for Medical Biometry, Informatics and Epidemiology (IMBIE) at the University of Bonn supervised by Andreas Mayr. Mark Coburn and Maria Wittmann supervised the score development and critically reviewed the manuscript. All authors read and approved the final manuscript.

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Declaration of Competing interest

Competing interests: none

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jclinane.2022.110684.

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3.2 Publication 2: Postoperative delirium after cardiac surgery of elderly patients as an independent risk factor for prolonged length of stay in intensive care unit and in hospital

Aging Clinical and Experimental Research https://doi.org/10.1007/s40520-021-01842-x

ORIGINAL ARTICLE

updates

Postoperative delirium after cardiac surgery of elderly patients as an independent risk factor for prolonged length of stay in intensive care unit and in hospital

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Abstract

Background Postoperative delirium (POD) is a relevant and underdiagnosed complication after cardiac surgery that is associated with increased intensive care unit (ICU) and hospital length of stay (LOS). The aim of this subgroup study was to compare the frequency of tested POD versus the coded International Statistical Classification of Diseases and Related Health Problems (ICD) diagnosis of POD and to evaluate the influence of POD on LOS in ICU and hospital.

Methods 254 elective cardiac surgery patients (mean age, 70.5 ± 6.4 years) at the University Hospital Bonn between Sep-tember 2018 and October 2019 were evaluated. The endpoint tested POD was considered positive, if one of the tests Con-fusion Assessment Method for ICU (CAM-ICU) or Confusion Assessment Method (CAM), 4 'A's Test (4AT) or Delirium Observation Scale (DOS) was positive on one day.

Results POD occurred in 127 patients (50.0%). LOS in ICU and hospital were significantly different based on presence (ICU 165.0 ± 362.7 h; Hospital 26.5 ± 26.1 days) or absence (ICU 64.5 ± 79.4 h; Hospital 14.6 ± 6.7 days) of POD ($p < 0.001$). The multiple linear regression showed POD as an independent predictor for a prolonged LOS in ICU (48%; 95%CI 31–67%) and in hospital (64%; 95%CI 27–110%) ($p < 0.001$). The frequency of POD in the study participants that was coded with the ICD F05.0 and F05.8 by hospital staff was considerably lower than tests revealed by the study personnel.

Conclusion Approximately 50% of elderly patients who underwent cardiac surgery developed POD, which is associated with an increased ICU and hospital LOS. Furthermore, POD is highly underdiagnosed in clinical routine.

Keywords Postoperative delirium · Cardiac surgery · Elderly patients · Diagnosis of delirium · Length of stay

Introduction

Postoperative delirium (POD) is an adverse and underdiag-nosed postoperative complication of elderly patients [1–3]. Data on the incidence of POD in surgical populations var-ies in a broad range from 11 to 51% [2]. Defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) and the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10), delirium is an acute and fluctuating disturbance of awareness, attention and cognition caused by an organic pathophysiology [4, 5]. In the literature, POD is divided into different forms, hyperactive, hypoactive and a mixture of both. Especially, the hypoactive delirium often remains undetected in the average clinical setting because of its characteristics such as unawareness, decreased alertness and decreased motor activity [6–10].

This study was conducted under the title: PRe-Operative Prediction of postoperative DElirium by appropriate SCreening (PROPDESC) and was registered in the German Registry for Clinical Studies under the following number DRKS00015715. Registered on 13th December 2018.

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Numerous risk factors are associated with the development of POD [11]. In addition to predisposing factors of the patient such as age, comorbidities, cognitive and functional impairment, the treatment of the patient like surgical invasiveness and duration of the operation are also causative for POD [2]. In the guideline of the European Society of Anaesthesiology for postoperative delirium, cardiovascular disease is described as a risk factor. It is also reported that comorbidities and a high degree of American Society of Anaesthesiologists (ASA) Physical Status Classification System pose a significant risk for POD [12]. Preoperative anaemia, as another surrogate marker for morbidity, is declared as a risk factor for POD as well as a predictor for a longer stay in hospital and in Intensive care unit (ICU) [12–16]. The combination of advanced age and comorbidities is often found in patients undergoing invasive and major cardiac surgery.

Many studies describe the increased risk of POD associated with cardiac surgery as 9–73% on average. This variability depends on several factors, such as the characteristics of the patients, the length of stay (LOS) in ICU and the delirium testing modalities. The difference between retrospective data collection using ICD codes and prospective daily testing for delirium by trained personnel is substantial [17–23]. Therefore, the subgroup analysis is focused on the comparison of the frequency of positively tested delirium compared to coded ICD (ICD-10-German Modification) diagnosis delirium in the same patient group.

The occurrence of postoperative delirium affects the workload of nursing staff and has a negative impact on patient outcomes. POD is associated with prolonged ICU and hospital stay, increased mortality and costs [9, 20, 22, 24–31]. To further investigate the influence of POD on LOS, this subgroup analysis includes possible surrogate parameters for morbidity that may influence both POD and LOS. Prolonged LOS in ICU poses a big burden on the limited resources of intensive care beds [32, 33]. Based on these results, the S3 guideline "Analgesia, Sedation and Delirium Management in Critical Care" calls for risk screening and preventive intervention and treatment of POD to reduce the incidence of delirium [34].

Therefore, the aim of this subgroup analysis was to measure the relationship of coded delirium diagnosis in comparison to the actual incidence of tested delirium in patients undergoing cardiac surgery. Furthermore, this study explored the severity of the diseases and analysed the impact of delirium on the length of ICU and hospital stay.

Methods

Study population

This prospective monocentre observational trial included 1098 patients from different surgical disciplines of the University Hospital Bonn. From September 2018 to October 2019, all patients, older than 60 years and with planned operations of at least 60 min duration, were considered eligible for the study. This study was conducted under the title: PRe-Operative Prediction of postoperative DElirium by appropriate SCreening (PROPDESC) and was registered in the German Registry for Clinical Studies under the following number DRKS00015715 [35]. The subgroup analysed here consists of all patients with cardiac surgery included in PROPDESC. The enrolled cohort of 308 patients consisted mainly of coronary artery bypass surgery (CABG), valve replacement or repair, or combined CABG with valve replacement or repair. Exclusion criteria included emergency procedures, language barriers or missing compliance with the study protocol. The present study complied within the principles of the declaration of Helsinki and was approved by the local institutional Ethics Committee at the Medical Faculty of the Rheinische Friedrich-Wilhelms-University of Bonn. Written informed consent was obtained from each patient.

Data collection

For each enrolled patient, 50 variables were collected. In this subgroup analyses, preoperative risk stratification such as ASA Physical Status Classification System, age, sex, number of medications, haemoglobin and the type of surgery were applied. Postoperative clinical variables were recorded including length of the intensive care unit stay (ICU-LOS) and LOS in the hospital. After discharge from the hospital, billing-relevant data such as the number of ICD codes and the severity of inpatient treatment were evaluated for each patient in the form of the German Patient Clinical Complexity Level (PCCL). In the German Diagnosis Related Group (G-DRG) classification, complications and/or comorbidities (CC) are mapped using the patient-related total severity code (PCCL). The PCCL is calculated from the cumulative severities of complications and/or comorbidities (CCL) of a patient's individual.

The data for the external comparison with regard to ICD-10-GM coding and the information on PCCL and LOS was taken from the Institut für das Entgeltsystem im Krankenhaus gGmbH (InEK) browser database 2019 [36]. The classification for postoperative delirium is listed in the ICD-10-GM Catalogue under Chapter V with the class title "Mental and Behavioural Disorders" under category

F05.- with the designation "delirious, not caused by alcohol or other psychotropic substances". The number of positive delirium results assessed by study personnel were compared to those coded by the hospital staff (ICD codes F05.0 and F05.8). To classify the individual cardiac surgery procedures, the German Operation and Procedure Code (OPS) classification 2019 was used.

Delirium assessment

Delirium assessments were conducted every morning by trained doctoral students on each of the first 5 days after surgery, respectively, on the first 5 days´ post-sedation. For this purpose, several standardized tests were used. To avoid missing delirium diagnosis in the context of spot examinations, the Delirium Observation Scale (DOS) was additionally applied by interviewing the nursing staff to assess the previous 24 h. Regarding the 5-day visit period, we used different test procedures for the intensive care and normal ward. Confusion Assessment Method for ICU (CAM-ICU) was used for intensive care patients. The Confusion Assessment Method (CAM) and the 4 'A's Test (4AT) were conducted in patients on the normal ward. The endpoint of a positive delirium diagnosis was considered to be fulfilled if one of the applied assessment methods detected POD on at least one of the 5 days. The aim of the overall PROPDESC study was to establish a sensitive risk score for postoperative delirium, thus different testing procedures were used in parallel to avoid missing any delirium abnormalities in the study cohort. Based on this subgroup analysis, the primary endpoint was maintained based on a positive test result from the various assessment tools. In accordance with good clinical practice, doctoral students were trained and monitored in the performance of each test at the beginning of the study. Regular quality assurance meetings were held throughout the study [35].

Data analysis

Statistical analysis was performed using the statistical programming environment R. Continuous and ordinal variables are presented with mean and ± standard deviation (sd). Nominal variables are displayed as numbers and percentages. Furthermore, the comparison between the delirium tested by trained study personnel and the coded delirium at the University Hospital Bonn and the average in Germany is presented by means of percentages. The grouping of individual procedures was performed on the basis of the billed diagnosis related groups (DRG). The same procedure was used to assess the LOS and the severity of treatment with PCCL.

Differences between the two groups (POD versus no POD) regarding preoperative factors were analysed using the non-parametric Mann–Whitney test for continuous variables. For categorical variables, Fisher's exact test was computed to check for independence.

To assess the independent effect of POD on LOS in ICU or in hospital, multi-variable linear regression analysis was performed to adjust for potential preoperative confounders. The LOS outcomes were log-transformed to ensure approximate normality of residuals. POD was entered as binary explanatory variable, while adjusting for preoperative surrogate parameters for morbidity (age, number of medication, ASA, preoperative haemoglobin value). To ensure interpretability, the coefficients of POD were re-transformed and are presented in percent increase (compared to non-POD) with corresponding 95% confidence intervals reflecting adjusted relative effects of POD on LOS.

Results

The subgroup included 308 patients, 14 (4.5%) patients were not operated, 15 (4.9%) patients died and 4 (1.3%) patients were still sedated when transferred to a further facility. 18 (5.8%) of the included patients received pacemaker or minimal invasive surgery and were removed from the analysed patient group based on the lack of complexity of the procedure. Three (1.0%) patients have withdrawn their consent and are, therefore, considered to be study dropout (Fig. 1). Thus, 254 patients with a mean age of 70.5 (± 6.4) years were included in the analyses. The gender distribution was 72 (28.4%) women and 182 (71.7%) men. We divided these patients into two groups based on the presence or absence of tested delirium: the POD group ($n = 127$, 50.0%) and the non-POD group ($n = 127$, 50.0%). For the evaluation on the basis of the billed DRG, one case is not included, since this case was billed with the previously performed pacemaker operation despite the heart valve operation.

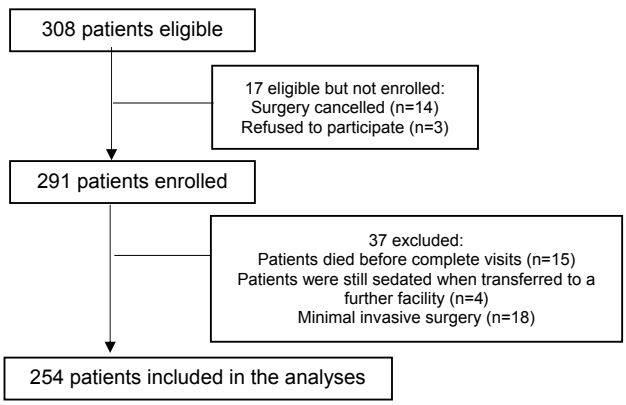

Fig. 1 Flowchart of subgroup patient selection

Procedural coding of POD

The ICD code F05.0 "Delirium without dementia" was coded 38 (15.0%) times in the included patient group of the University Hospital Bonn and the diagnosis F05.8 "Other form of delirium" was coded 15 (5.9%) times. Among the F05.0 positively coded patients, 33 (86.8%) were tested positive by the study personnel in the specified assessment window and 14 (93.3%) of the F05.8 coded patients have also been tested positive. The percentage of positive POD patients in PROPDESC is consistently higher than the coded diagnoses in the University Hospital Bonn and the German average (Table 1). The tested delirium incidence ranges from an average of 35.5% up to 100%. In our trial, we found a rate of positive tested delirium for patients with heart valve surgeries of 58.5%, whereas the InEK data of coded ICD diagnoses for delirium was in total 14.3% in this group of patients. For CABG patients in our trial the incidence of delirium was 35.6%, whereas the InEK shows an average percentage of 18.7%. In addition, we found that the percentage frequency of coded delirium diagnoses at the University

Table 1 Distribution of ICD codes and positive POD test results

		Total	POD group		POD group
			F05.0	F05.8	PROPDESC
		n	% (n)	% (n)	% (n)
Heart valve surgery					
	University hospital	94	14.9 (14)	3.2 (3)	58.5 (55)
	InEK database	5,929	2.8	11.5	
CABG					
	University hospital	87	8.1 (7)	3.5 (3)	35.6 (31)
	InEK database	6,870	3.8	14.9	
Complex intervention					
	University hospital	7	0.0	14.3 (1)	71.4 (5)
	InEK database	1,575	1.2	8.9	
ICU complex treatment					
	University hospital	10	60.0 (6)	20.0 (2)	90.0 (9)
	InEK database	1,730	9.3	23.2	
Ventilation > 24 h					
	University hospital	31	12.9 (4)	6.5 (2)	35.5 (11)
	InEK database	1,366	5.6	13.0	
Ventilation > 95 h					
	University hospital	13	23.1 (3)	0.0	38.5 (5)
	InEK database	4,075	7.3	16.0	
Ventilation > 249 h					
	University hospital	4	50.0 (2)	0.0	75.0 (3)
	InEK database	2,731	8.8	14.6	
Ventilation > 499 h					
	University hospital	3	33.3 (1)	33.3 (1)	100.0 (3)
	InEK database	180	13.9	15.0	
Ventilation > 1799 h					
	University hospital	4	25.0 (1)	50.0 (2)	100.0 (4)
	InEK database	83	18.8	22.1	

This table shows the relative frequency of coded delirium diagnoses (ICD F05.0 and F05.8) at the Bonn University Hospital and in the InEK database, as well as the relative frequency of positively tested delirium patients. For ease of comparison, the individual billing codes (DRGs) are grouped under the terms of the main interventions. The following DRGs are summarized under the respective main interventions: Heart valve surgery included DRGs: F03A-F03C, F03E-F03F; CABG included DRGs: F05Z, F06A-F06E; Complex intervention included DRGs: F07B-F07C; ICU complex treatment included DRGs: F36A-F36C; Ventilation > 24 h included DRG: F43B; Ventilation duration > 95 h included DRGs: A13A, A13D-A13E; Ventilation duration > 249 h included DRGs: A11A-A11B, A11E; Ventilation duration > 499 h included DRG: A09A; Ventilation > 1799 h included DRGs: A06A-A06B

POD postoperative delirium, CABG coronary artery bypass grafting, ICU intensive care unit, InEK Institut für das Entgeltsystem im Krankenhaus gGmbH

Hospital Bonn (CABG 11.5%; heart valve surgery 18.1%) was considerably lower than that of the same patients who were tested positive by study personnel (CABG 35.6%; heart valve surgery 58.5%). In addition to the ICU complex treatments, the combination procedures involving CABG and heart valve surgery (71.4%) showed the highest tested delirium incidence.

Comparison of comorbidity

The average severity of disease, expressed in PCCL, was not predominantly higher in university hospital patients than in the patients in the InEK comparison (Table 2). This is explained by the fact that most cardiac surgeries are performed at university hospitals and therefore the severity of the InEK patients is similar to the severity of the patients examined here. Within the entire subgroup, 188 (74.3%) patients were billed on the basis of cardiac surgery and 65 (25.7%) on the basis of the more complex intensive care treatment after the cardiac surgery. The presence of delirium showed statistically significant differences in the preoperatively determined haemoglobin value (no delirium: 14.0 ± 1.6 g/dl; delirium: 13.4 ± 1.8 g/dl; $p < 0.009$), the number of ICD codes (no delirium: 13.5 ± 5.3; delirium

Table 2 List of severity levels by *Patient Clinical Complexity Level (*PCCL) and average length of stay (LOS)

		Total	LOS in hospital (days)	PCCL 0	PCCL 1	PCCL 2	PCCL 3	PCCL 4	PCCL 5	PCCL 6
		N	mean	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)
Heart valve surgery										
	University hospital	94	18.6	20.2 (19)	1.1 (1)	7.5 (7)	35.1 (33)	26.6 (25)	9.6 (9)	0.0 (0)
	InEK database	5,929	14.5	19.2	6.5	14.2	28.4	23.8	7.8	0.2
CABG										
	University hospital	87	15.1	10.3 (9)	10.3 (9)	21.8 (19)	31.0 (27)	18.4 (16)	8.1 (7)	0.0 (0)
	InEK database	6,870	19.0	8.2	6.6	11.7	21.2	34.8	16.3	1.3
Complex intervention										
	University hospital	7	13.6	14.3 (1)	0.0 (0)	0.0 (0)	28.6 (2)	42.9 (3)	14.3 (1)	0.0 (0)
	InEK database	1,575	13.5	14.7	3.9	9.4	28.3	28.4	14.4	1.0
ICU complex treatment										
	University hospital	10	30.8	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	40.0 (4)	50.0 (5)	10.0 (1)
	InEK database	1,730	29.6	0.5	1.0	1.9	13.8	33.1	41.8	8.0
Ventilation > 24 h										
	University hospital	31	15.8	0.0 (0)	3.2 (1)	16.1 (5)	54.8 (17)	25.8 (8)	0.0 (0)	0.0 (0)
	InEK database	1,366	17.6	2.3	3.3	10.4	35.5	45.6	2.9	0.0
Ventilation > 95 h										
	University hospital	13	23.5	0.0 (0)	7.7 (1)	7.7 (1)	53.9 (7)	23.1 (3)	7.7 (1)	0.0 (0)
	InEK database	4,075	23.1	3.7	3.1	6.3	28.4	42.0	16.2	0.2
Ventilation > 249 h										
	University hospital	4	32.3	0.0 (0)	0.0 (0)	25.0 (1)	0.0 (0)	50.0 (2)	25.0 (1)	0.0 (0)
	InEK database	2,731	34.3	2.7	2.7	7.1	27.8	37.8	20.5	1.4
Ventilation > 499 h										
	University hospital	3	93.7	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	66.7 (2)	33.3 (1)
	InEK database	180	58.5	0.0	0.0	0.6	2.2	25.0	61.1	11.1
Ventilation > 1799 h										
	University hospital	4	132.8	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	25.0 (1)	75.0 (3)
	InEK database	83	111.9	0.0	0.0	0.0	3.5	7.6	39.5	49.3

This table shows the comparison of the Patient Clinical Complexity Level (PCCL) of the tested patients of the University Hospital Bonn and the data of the InEK. For ease of comparison, the individual billing codes (DRGs) are grouped under the terms of the main interventions. The following DRGs are summarized under the respective main interventions: Heart valve surgery included DRGs: F03A-F03C, F03E-F03F; CABG included DRGs: F05Z, F06A-F06E; Complex intervention included DRGs: F07B-F07C; ICU complex treatment included DRGs: F36A-F36C; Ventilation > 24 h included DRG: F43B; Ventilation duration > 95 h included DRGs: A13A, A13D-A13E; Ventilation duration > 249 h included DRGs: A11A-A11B, A11E; Ventilation duration > 499 h included DRG: A09A; Ventilation > 1799 h included DRGs: A06A-A06B

PCCL German Patient Clinical Complexity Level, LOS length of stay, InEK Institut für das Entgeltsystem im Krankenhaus gGmbH, CABG coronary artery bypass grafting, ICU intensive care unit

18.5 ± 10.3; $p < 0.001$) and the level of PCCL (no delirium: 2.6 ± 1.4; delirium 3.4 ± 1.5; $p < 0.001$) after discharge from hospital (Table 3). The ASA classification, number of different medication taken before surgery and age of the patients did not differ significantly between the delirious and non-delirious patients. The mean age was 70.9 (± 6.4) years for the delirious patients and 70 (± 6.3) years for the non-delirious patients. Based on their underlying cardiac disease, 77% (n = 195) of patients were grouped with ASA 3 (Table 3).

Relationship between delirium and LOS

Table 2 compares the average LOS of patients of the PROP-DESC study patients at the University Hospital Bonn with the average LOS of patients in the InEK database. Patients at the University Hospital had different LOS (valve surgery 18.6 days; CABG 15.1 days) compared to the mean value of the InEK population (valve surgery 14.5 days; CABG 19.0 days). Patients manifesting delirium had a significantly longer LOS in hospital (no delirium: 14.6 ± 6.7 days; delirium 26.5 ± 26.1 days; $p < 0.001$) (Table 3). Furthermore, the study results display that patients with a POD are hospitalized on average 12 days longer (Table 3). The study results confirm that the LOS in hospital is nearly twice as long in patients with POD after cardiac surgery (26.5 ± 26.1 days) compared to the average LOS of this patient group (14.6 ± 6.7 days). The results of the linear regression model support this statement (Table 4). They showed that patients with POD have a 48% (95% CI 31–67%) increase in LOS in hospital even when adjusting for potential confounders.

In addition to this, the study results demonstrate that patients with delirium had a significantly longer ICU LOS (no delirium: 64.5 ± 79.4 h; delirium 165.0 ± 362.7 h; $p < 0.001$) (Table 3). In total, the delirious study patients had a 2.5 times longer intensive care stay than the group of

Table 4 POD as an independent predictor for LOS in the ICU and in hospital: effects were adjusted for preoperative risk factors via a multi-variable linear regression model and are presented as increase in percent

	POD (adj. effect)	95% CI	*p* value
LOS in ICU (hours)	+ 48%	+ 31% to + 67%	< 0.001
LOS in hospital (days)	+ 64%	+ 27% to + 110%	< 0.001

POD postoperative delirium, CI Confidence Interval, ICU intensive care unit, LOS length of stay

POD effect adjusted for preoperative surrogate parameters for morbidity (age, number of medication, ASA, preoperative haemoglobin value)

Table 3 Perioperative risk factors for POD

	Total	POD group	Non-POD group	*p* value
No. (%)	254	127 (50.0)	127 (50.0)	-
Age (years)	70.5 ± 6.4	70.9 ± 6.4	70.0 ± 6.3	0.229
No. of coded ICD	16.0 ± 8.6	18.5 ± 10.3	13.5 ± 5.3	< 0.001
No. of medication	6.1 ± 2.9	6.3 ± 3.0	5.9 ± 2.8	0.196
Haemoglobin (g/dl)	13.7 ± 1.7	13.4 ± 1.8	14.0 ± 1.6	0.009
Level of PCCL	3.0 ± 1.5	3.4 ± 1.5	2.6 ± 1.4	< 0.001
PCCL level 0		7.0 (9)	15.9 (20)	
PCCL level 1		3.9 (5)	5.6 (7)	
PCCL level 2		11.7 (15)	14.3 (18)	
PCCL level 3		26.8 (34)	40.9 (52)	
PCCL level 4		28.9 (37)	19.8 (25)	
PCCL level 5		17.2 (22)	4.0 (5)	
PCCL level 6		3.9 (5)	0.0 (0)	
Level of ASA	3.2 ± 0.5	3.2 ± 0.5	3.2 ± 0.5	0.638
ASA level 1		0.8 (1)	0.0 (0)	
ASA level 2		1.6 (2)	4.0 (5)	
ASA level 3		77.2 (98)	76.4 (97)	
ASA level 4		20.3 (26)	19.8 (25)	
LOS in hospital (days)	20.6 ± 20.0	26.5 ± 26.1	14.6 ± 6.7	< 0.001
LOS ICU (hours)	114.8 ± 266.8	165.0 ± 362.7	64.5 ± 79.4	< 0.001

POD postoperative delirium, PCCL German Patient Clinical Complexity Level, ASA American Society of Anaesthesiologists, LOS length of stay, ICU intensive care unit

Data are expressed as mean ± standard deviation. The frequencies of the individual levels of PCCL and ASA are shown in percent and (= n)

patients without delirium. The average time difference was 100 h and was caused by the fact that study patients with delirium stayed 4.2 days longer in ICU. The results of the linear regression confirm delirium as an independent predictor of LOS in ICU (Table 4). Following our model, patients with POD have a 64% (95% CI: 27–110%) increase in LOS in ICU independently from their preoperative risk factors.

Discussion

POD is a common complication of elderly patients after cardiac surgery and has a high impact on LOS in ICU and hospital. Furthermore, the secondary diagnosis of POD is clearly underdiagnosed, demonstrating the extent to which this secondary diagnosis is underestimated. The incidence in the present study was 50.0% and thus in between the 9% and 73% stated in the literature [17–23]. Explanations for this variability in the literature could be a different extent and different instruments of studies to assess POD [11]. While PROPDESC used several tools (two for ICU and three on normal ward) other studies evaluated POD with one tool or used the retrospective analysis of ICD codes. In this study, we compared the number of positive tested delirious patients (from 35.5 to 100%) with the coded delirious diagnosis (ICD F05.0 and F05.8) in the University Hospital Bonn and the German-wide average (from 10.3 to 40.9%). We found that the percentage frequency of reported delirium diagnoses in the considered group of patients was significantly lower than as tested positive by study personnel. The difference was 40.4% for heart valve surgery and 24.1% for CABG. There are several explanations for this significant difference. Prior work has described a range up to 80% of the hypoactive subtype of delirium [6, 10, 20, 23, 37, 38]. These results suggest that the form of hypoactive POD often remains undetected by hospital staff and is, therefore, not so present in the reported ICDs. Furthermore, this could also lead to the assumption that there is no standardized delirium testing, as pointed-out by various studies and guidelines [12, 39–45]. It should also be noted that in the German DRG system, the share of material costs for heart valve surgery and CABG, accounts for more than a quarter of total costs (heart valve surgery F03A-F03F 30–37% material costs; CABG F05Z, F06A-F06E 23–30% material costs) [36]. Considering the high material costs, the coding of delirium does not result in a relevant surcharge and might be, therefore, neglected as a complication and comorbidity. This leads to the conclusion that from a medico-economic perspective there is no incentive to diagnose POD. However, various examples can be found in the existing literature that the nursing effort in combination with a POD increases significantly and thus, the cost-relevant effort as well [9, 20, 46].

Prior work has documented that a high number of comorbidities, severe diseases and advanced age occur more frequently among the delirious patients [12]. Our data confirm the results of previous studies that comorbidities have an influence on the development of POD which is shown by the significantly higher number of ICD codes and PCCL of delirious patients [2, 12, 20, 38]. However, we could not find a significant difference between the POD and the non-POD groups in terms of age, number of preoperative medication and ASA classification preoperatively. So far, only few studies have dealt with the hypothesis whether patients have a more complex and longer course of inpatient treatment due to delirium, or whether the present morbidity is the main reason for this. One study confirmed that the prolonged intensive care stay of cardiac surgery patients is based on the complication of POD and not on the pre-existing morbidity [20]. However, POD is very often recognized as an effect on ICU LOS and length of hospital stay [20, 47–51]. In this study, we were able to show that POD is independently associated with an increased LOS in ICU and in hospital among patients undergoing cardiac surgery and, also an extended length of hospital stay compared to the German average. Based on the PCCL comparison between the PROPDESC patients and the German average, the argument that the study population is sicker and, therefore, has a longer stay is not supported by the results of our analysis. On the contrary, we were able to confirm via multiple linear regression that POD has an independent effect on LOS after adjusting for preoperative surrogate parameters for morbidity.

Although the results of this subgroup study analysis demonstrate causality only for surrogate parameters, they underline the importance of detection of POD in elderly cardiac surgery patients. Delirium poses additional work on the nursing staff and prolongs the duration of the ICU stay by an average of 4.2 days. If German hospitals would introduce standardized preoperative risk screening and prevention programmes to increase the awareness of a possible POD, the incidence of delirious patients might be reduced [52–56]. If standardized screening with containment prevention and therapy of POD could reduce the LOS in ICU, this would have a considerable impact on the limited capacities of German intensive care units. Among the 254 patients included in this study over the period of 1 year, approximately 50% were delirious after their surgery. A reduction of the LOS of this patient group by one day (from an average of 7 to 6 days) would result in the free capacity of an intensive care bed for 127 days per year. According to the University Hospital Bonn's quality report, 720 CABG and heart valve surgeries were performed in 2018. If an extrapolated 50% of the patients in the total population had shown delirium, this would have resulted in 360 patients. By reducing the LOS on ICU by only 1 day, the capacity of one bed in a

12-bed ICU would be available for about 1 year (360 days) for additional patients.

Based on the results of this study POD has an impact on LOS in ICU and is rarely diagnosed in clinical routine. If the delirium diagnosis does not have a relevant influence on the billing amount, the reduction of the incidence of delirium should be focussed on medical-economic aspects to improve the capacity utilization of the bottleneck in ICUs.

Study limitation

This study has several limitations. One limitation is the small sample size, related to the character of the subgroup analyses. In connection with the regression analysis, there might be unknown confounding factors for which we were not able to adjust for. These factors could additionally influence both POD and the LOS. Furthermore, the delirious PROPDESC patients were only based on the result of a positive test result of the study staff and has no delirium diagnosis by a psychologist. The comparison with the nationwide ICD diagnoses of POD and other data from the InEK browser database is based on data from 2019, but the patients of this subgroup were enrolled during 2018 and 2019. Based on the coding guidelines, only ICDs with associated inpatient treatment costs are coded and, therefore, do not represent the total comorbidities of patients. In addition, the summarized Tables with the DRG overview do not clearly show which interventions the intensive complex treatments are based on.

Conclusion

Postoperative delirium is associated with a significantly increased LOS in hospital as well as ICU. The frequency of ICD coding of POD in the subgroup analysis as well as in the internationally available accounting data is considerably lower than the tested incidence of POD. Based on the underlying billing system, there is no financial incentive for ICD coding of POD in cardiac surgery patients, so this could be a possible reason for the low coding rate of this secondary diagnosis. Future research should evaluate the introduction of standardized, fast and simple preoperative risk screening followed by prevention programmes to reduce the incidence of delirium and its impact on LOS.

Authors' contributions VG, JM and MW contributed to the development of the original protocol; MC critically reviewed the trial protocol; JM is the PI of the study; AK and JF contributed to patient recruitment; MW and AK are responsible for the design of this sub-study; AK performed the descriptive and bivariate analyses and wrote the first draft; AM performed the regression analyses; all authors critically reviewed the manuscript for important intellectual content and approved the final version submitted for publication.

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Availability of data and materials The data sets generated and/or analysed during the study are available on request from the corresponding author.

Code availability The R code used for the analysis is available on request from the corresponding author.

Declarations

Conflicts of interest The authors declare no conflict of interest.

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of University Bonn (Ethics Committee at the Medical Faculty of the Rheinische Friedrich-Wilhelms-University of Bonn) (Date 18.09.2017/No. 255/17 Ethical Approval Document 1). The study protocol including amendments was finalized on 2nd of May 2018 as version 2.1 (Ethical Approval Document 2).

Informed consent Each patient has given written informed consent to participate in the study.

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3.3 Publication 3: Postoperative delirium is an independent factor influencing the length of stay of elderly patients in the intensive care unit and in hospital

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ORIGINAL ARTICLE

Postoperative delirium is an independent factor influencing the length of stay of elderly patients in the intensive care unit and in hospital

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Abstract

Purpose Postoperative delirium (POD) is an often unrecognized adverse event in older people after surgery. The aim of this subgroup analysis of the PRe-Operative Prediction of postoperative DElirium by appropriate SCreening (PROPDESC) trial in patients aged 70 years and older was to identify preoperative risk factors and the impact of POD on length of stay (LOS) in intensive care unit (ICU) and hospital.

Methods Of the total 1097 patients recruited at a German university hospital (from September 2018 to October 2019) in the PROPDESC prospective observational study, 588 patients aged 70 years and older (mean age 77.2 ± 4.7 years) were included for subgroup analysis. The primary endpoint POD was considered positive if one of the following tests were posi-tive on any of the five postoperative visit days: Confusion Assessment Method for ICU (CAM-ICU), Confusion Assessment Method (CAM), 4'A's (4AT) and Delirium Observation Scale (DOS). Trained doctoral students carried out these visitations and additionally the nursing staff were interviewed for completion of the DOS. To evaluate the independent effect of POD on LOS in ICU and in hospital, a multi-variable linear regression analysis was performed.

Results The POD incidence was 25.9%. The results of our model showed POD as an independent predictor for a prolonged LOS in ICU (36%; 95% CI 4–78%; < 0.001) and in hospital (22%; 95% CI 4–43%; < 0.001).

Conclusion POD has an independent impact on LOS in ICU and in hospital. Based on the effect of POD for the elderly, a standardized risk screening is required.

Trail registration German Registry for Clinical Studies: DRKS00015715.

Keywords Postoperative delirium · Elderly patients · Length of stay

Introduction

The older generation will continue to grow steadily in the coming years. In 2050, the number of people aged 70 and older will nearly have doubled from 5.9 to 11.3% [1]. With increasing age, people suffer more frequently from diseases and often develop multimorbidity [2]. Additionally, the inci-dence of cognitive impairment in the elderly is also not to be underestimated. Severity of illness, cognitive impairment, as well as functional, visual, and hearing impairment, are considered risk factors for postoperative delirium in literature [3–8].

Postoperative delirium (POD) is an often unrecognized postoperative adverse event in the elderly [3, 9–11]. Defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) and the 10th revision of the International Statistical Classification of Disease and Related Health Problems (ICD-10), delirium is an acute and fluctuating disturbance of awareness, attention and cognition caused by an organic pathophysiology [12, 13]. In the literature, the clinical presentation of POD is divided into hypoactive, hyperactive and mixed forms. Whereas the occurrence of hypoactive delirium is often underestimated in everyday clinical practice, hyperactive delirium makes patient´s care very time-consuming [14–16].

The incidence of POD varies in different surgical populations from 11 to 51% [3, 9, 10]. In addition to various

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outcome deteriorations such as cognitive impairment and other postoperative complications, the effects of POD on the length of stay (LOS) are also often reported [17–20]. Regardless of the complication of POD, prolonged length of stay is often mentioned as an cost-increasing factor in various studies of patients who underwent surgery [21].

In conjunction with a prolonged hospital stay, elderly patients, in particular, may experience additional loss of function that can severely impact the ability to continue an independent life [22]. However, the prolonged stay and complication of POD is not only a burden for patients, but also for nurses [23]. Furthermore, it is commonly known that there is a shortage of nurses and physicians in hospitals. Thus, there is a limited human resource for high-quality care of elderly patients. For all intents and purposes, this means that a prolonged length of stay in combination with a POD puts a strain on the limited resources and makes it even more difficult to provide needs-based care for older affected people [24]. POD is a postoperative complication influenced by various perioperative risk factors, which can be counteracted protectively [5].

This subgroup analysis was performed to figure out the risk factors for POD (age, surrogate parameters for multimorbidity, surgery associated risk factors) in the elderly in more detail and to take a closer look at the effects of these factors on the length of stay. Further, this analysis will examine whether POD is an independent risk factor for a prolonged stay in an intensive care unit (ICU) and in hospital.

Materials and methods

Study design and participants

This is a subgroup analysis of an observational prospective single-centre trial on patients from different surgical disciplines of the University Hospital Bonn. The entire study, conducted from September 2018 to October 2019 under the title "PRe-Operative Prediction of postoperative DElirium by appropriate SCreening (PROPDESC)" included 1097 patients [25]. It was registered in the German Registry for Clinical Studies under the number DRKS00015715 and was approved by the local institutional Ethics Committee at the Medical Faculty of the Rheinische Friedrich-Wilhelms-University of Bonn. Written informed consent was obtained from each patient. Patients with age 60 and older and with a planned surgery duration of at least 60 min were eligible for the PROPDESC study. Exclusion criteria were emergency procedures, language barriers or missing compliance with the study protocol.

The subgroup analyzed here included all enrolled patients aged 70 and older. The patient data pertain to the inpatient period and the discharge date.

Data collection

In this subgroup analysis, 15 variables were included. Preoperative data collected include the following: age, sex, body-mass-index (BMI), cognitive impairment tested with the Montreal Cognitive Assessment (MoCA), hearing impairment (yes or no), POD in the medical history (yes or no), the number of long-term medication, American Society of Anesthesiologists (ASA) Physical Status Classification System, Revised Cardiac Risk Index (rCRI), New York Heart Association Classification (NYHA), Metabolic Equivalent of Tasks (MET), surgical risk and surgical discipline. Surgical risk was transformed from a 5-level Johns-Hopkins classification to the 3-level modified Johns-Hopkins surgical criteria [26, 27]. Intraoperative data collected include red blood cell transfusion and ventilation time. Postoperative data collected include surgery duration, length of stay (LOS) in the intensive care unit (ICU) and LOS in hospital.

Patient outcome

The primary endpoint of POD was assessed on the first five consecutive days after surgery, alternatively after the end of sedation. Sedated patients with RASS [28] score < -3 were considered as not assessable and therefore their testing for POD was initiated after exceeding this level of sedation according to Confusion Assessment Method for ICU (CAM-ICU) [29].

Trained doctoral students performed the testing. In order not to miss a positive POD diagnosis, different tests were applied in the PROPDESC study. CAM-ICU was used for intensive care patients and Confusion Assessment Method (CAM) and the 4 'A's (4AT) were conducted in patients on the normal ward [29–31]. To avoid missing delirium diagnosis in the context of spot examinations, the Delirium Observation Scale (DOS) was additionally applied by interviewing the nursing staff to assess the previous 24 h [32]. The positive endpoint POD was considered if one of the applied delirium assessments was positive on at least one visit day. The definition of completed POD assessment required a valid conduct of at least three of the five scheduled postoperative visits. Discharge home before the third visit was accepted as an exception to this rule, on the assumption that patients would not subsequently become delirious in their familiar environment.

Statistical analysis

Statistical analysis was performed using the statistical programming environment R. Continuous and ordinal variables are presented with mean and standard deviation (SD±).

Nominal variables are displayed as numbers and percentages. Patients were divided into two groups (non-POD vs. POD group) based on the POD endpoint. The difference between these groups regarding the characteristics was analyzed using the non-parametric Wilcoxon rank-sum test for continuous variables. For categorical variables, Fisher´s exact test was computed to check for independence.

To evaluate the independent effect of POD on LOS in ICU and in hospital, a multi-variable linear regression analysis was performed to adjust for various perioperative potential confounders. The LOS outcomes were log-transformed to ensure approximate normality of residuals. POD was entered as a binary variable while adjusting for perioperative risk factors for POD. These covariates were preoperative age, ASA, NYHA, MET, rCRI classification levels, MoCA sum score, hearing impairment, history of delirium, number of medication and intra-/postoperative surgical risk, surgical discipline, duration of surgery, red cell blood transfusion and ventilation time. In conjunction with the multivariable linear regression analysis related to the effect of POD on LOS in ICU, only patients in the cohort who actually had an ICU stay were included and ventilation time was removed in the risk adjustment because it contains part of the outcome parameter LOS in ICU. To ensure the interpretability, the coefficients of POD from modelling the log LOS were re-transformed and are presented in the percent increase (compared to non-POD) with a corresponding 95% confidence interval. For sensitivity reasons, the regression analyses were repeated also without covariates, which contained more than 5% missing values to check for potential biases induced due to the missing observations.

Results

The subgroup of patients aged ≥ 70 years included 668 patients. Of this cohort, 52 (7.8%) patients had no surgery and one (0.1%) has withdrawn the consent during the observation period. Of the 615 patients enrolled, an additional nine (1.3%) died within the postoperative visitation period without reaching the positive endpoint of POD. Since the complete assessment of the primary endpoint of POD was not possible, these patients were also removed from the dataset. Furthermore, 18 (2.7%) patients had less than three visits completed before postoperative day 5 without having been discharged from the hospital. These patients were also removed from the evaluation cohort, and thus 588 patients were included in the analyses presented here. The flow chart (Fig. 1.) shows the case number of participants and their exclusion criteria.

Characteristics of perioperative variables related to POD

The mean age of the subgroup analyzed here was 77.2 (± 4.7) years and the gender distribution was 248 (42.2%)

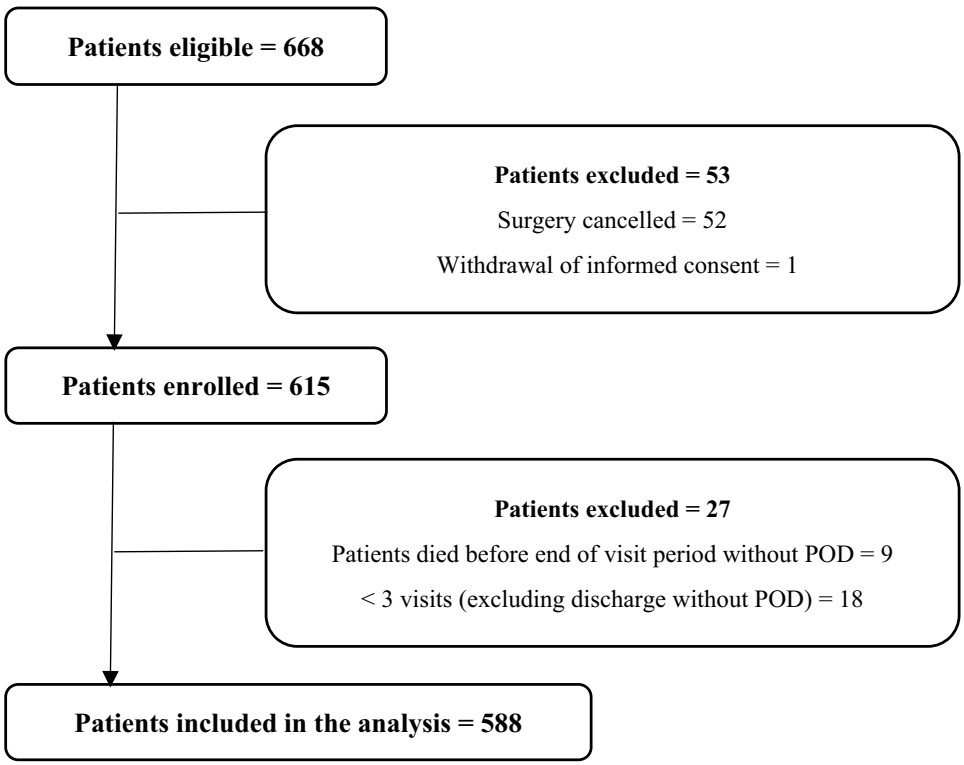

Fig. 1 Flow chart

women and 340 (57.8%) men. POD incidence was 25.9% (152). Table 1 shows the variables collected preoperatively and postoperatively divided into the non-POD and POD groups. Anesthetic classifications (ASA, $p < 0.001$; NYHA, $p < 0.001$; MET, $p = 0.009$ and rCRI, $p < 0.001$) were significantly different between the delirious and non-delirious groups. Furthermore, POD patients (21.4 ± 4.1) showed a significantly lower MoCA sum score than non-POD patients (22.8 ± 3.7; $p < 0.001$). The surgical risk of the cohort was significantly higher in patients who developed POD postoperatively. As expected the highest POD incidence occurred in patients after cardiac surgery with 52.6% (80). Postoperative variables also differed significantly between the delirious and non-delirious groups. POD patients had an average of 78 min longer surgery duration (non-POD 188.9 ± 115.1; POD 266.8 ± 121.9; $p < 0.001$). Furthermore, the duration of ventilation differed by about 25 h. In the non-delirious patients, the mean value of ventilation time was 7 h (7.44 ± 13.4) and in the delirious patients about 32 h (32.2 ± 24.8; $p < 0.001$). The length of intensive care stay differed by an average of 138 h between delirious (21.4 ± 62.4) and non-delirious patients (159.3 ± 525.4; $p < 0.001$). This makes a difference in the LOS in ICU of about 6 days. Also shown was a significant difference in total LOS in the hospital of about 8 days. Patients who developed POD during the visit period stayed about 26 days (25.6 ± 17.2) and patients without POD stayed an average of 17 days (17.2 ± 25.7; $p < 0.001$).

Characteristics of perioperative variables related to a postoperative ICU stay

To obtain a more accurate overview of the cohort that was postoperatively in intensive care, the subgroup was divided into two groups (non-ICU and ICU). Table 2 compares the intraoperative variables and the postoperative POD-Outcome for the ICU (267; 45.4%) and non-ICU (313; 53.2%) group. The average stay of intensive care patients was 123.4 h (± 399.4). Fifty-five point four percent (148) of the patients on ICU underwent cardiac surgery and 71.5% (191) had a high-risk surgery. Patients with a postoperative intensive care stay showed an average of 149 min longer surgery duration (non-ICU 140.9 ± 77.6 min; ICU 290.1 ± 114.9 min; $p < 0.001$). Furthermore, the two groups differed significantly in red blood cell transfusion (non-ICU 51.1 ± 277.4 ml; ICU 856.0 ± 2136.6 ml; $p < 0.001$) and ventilation time (non-ICU 3.6 ± 1.5 h; ICU 26.0 ± 95.7 h; $p < 0.001$). The non-ICU and ICU groups also differed significantly in postoperative outcomes related to POD and overall LOS in hospital. Forty-two point three percent (113) of intensive care patients developed POD and only 11.5% (36) of non-intensive care patients were tested positive. Patients with ICU stay showed an average of 9 days longer total hospital stay (non-ICU 15.4 ± 20.6 days; ICU 24.0 ± 30.3 days; $p < 0.001$).

Influence of POD on LOS in ICU and in hospital

Linear regression results confirm POD as an independent predictor of LOS in the ICU after risk adjustment with perioperative variables (Table 3). Following our model, patients with POD have a 36% (95% CI 4–78%; $p < 0.001$) increase in LOS in ICU independently from their perioperative risk factors. A sensitivity analysis fitting the same regression model without the variable red blood cell transfusion (which contains $n = 66$ missing values) led to very similar results (43% increase; 95% CI 10–86%; $p < 0.001$). Furthermore, the linear regression model confirms that patients with a POD have a 22% (95% CI 4–43%; $p < 0.001$) increase in LOS in hospital after adjusting with perioperative variables. Again, the sensitivity analysis without adjusting for red blood cell transfusion supports this (25% increase; 95% CI 8–45%; $p < 0.001$).

Discussion

POD incidence and predictors

The POD incidence in this subgroup analyses with patients aged 70 and older was 25.9%. Several preoperative variables showed a significant difference between the POD and non-POD groups. As confirmed in the literature, there was a significant difference in preoperative cognitive testing with the MoCA and positive POD assessment [3–5, 33, 34]. In addition, further studies have shown that cognitive impairment may also have an impact on prolonged hospital stay [35]. However, cognitive impairment as a major preoperative risk marker for POD has been strongly described in systematic reviews as well as in the ESAIC Guideline. Based on the preoperative anesthetic classifications (ASA, NYHA, MET, rCRI), the patients who developed POD were also classified with more pre-existing clinically relevant conditions. Furthermore, the preoperative assessed surgical risk was on average higher in the POD group than in the non-POD group. The ESAIC guidelines recommend, based on their systematic analysis of the study evidence, that ASA classification should be considered a pre-operative risk marker for POD. Furthermore, it is recommended that the factor of surgical risks should also be considered in the risk analysis for POD. These findings are congruent with the POD risk factors described in literature and guidelines [5, 36]. Contrary to what has been reported in the literature, the POD patients in this subgroup did not show significant differences in hearing impairment and a prior POD experience, relative to the non-POD group [37].

Table 1 Pre- and postoperative variables for the non-POD and POD group

Characteristics	Total	Non-POD	POD	*p* value	Missing values
No	588	436 (74.2)	152 (25.9)	–	–
Age	77.2 ± 4.7	77.1 ± 4.8	77.5 ± 4.6	0.245	0
Sex (no., %)				0.013	0
Female	248 (42.2)	197 (45.2)	51 (33.6)		
Male	340 (57.8)	239 (54.8)	101 (66.5)		
BMI	27.0 ± 4.9	27.0 ± 5.0	27.0 ± 4.6	0.688	1
No. of medication	6.0 ± 3.7	5.8 ± 3.7	6.6 ± 3.6	0.011	10
Hearing impairment				0.354	0
Yes	175 (29.8)	125 (28.7)	50 (32.9)		
No	413 (70.2)	311 (71.3)	102 (67.1)		
History of POD				0.858	1
Yes	44 (7.5)	32 (7.3)	12 (7.9)		
No	543 (92.4)	403 (92.4)	140 (92.1)		
MoCA sum	22.4 ± 3.8	22.8 ± 3.6	21.4 ± 4.1	< 0.001	0
ASA (no., %)				< 0.001	0
ASA 1	9 (1.5)	7 (1.6)	2 (1.3)		
ASA 2	190 (32.3)	168 (38.5)	22 (14.5)		
ASA 3	344 (58.5)	238 (54.6)	106 (69.7)		
ASA 4	45 (7.7)	23 (5.3)	22 (14.5)		
rCRI (no., %)				< 0.001	0
rCRI 1	237 (40.3)	207 (47.5)	30 (19.7)		
rCRI 2	141 (24.0)	105 (24.1)	36 (23.7)		
rCRI 3	146 (24.8)	94 (21.6)	52 (34.2)		
rCRI 4	64 (10.9)	30 (6.9)	34 (22.4)		
NYHA (no., %)				< 0.001	0
NYHA I	235 (40.0)	199 (45.6)	36 (23.7)		
NYHA II	203 (34.5)	152 (34.9)	51 (33.6)		
NYHA III	137 (23.3)	78 (17.9)	59 (38.8)		
NYHA IV	13 (2.2)	7 (1.6)	6 (4.0)		
MET (no., %)				0.009	0
MET < 1	9 (1.5)	7 (1.6)	2 (1.3)		
MET 1–4	307 (52.2)	210 (48.2)	97 (63.8)		
MET 5–10	255 (43.4)	205 (47.0)	50 (32.9)		
MET > 10	17 (2.9)	14 (3.2)	3 (2.0)		
Surgical discipline (no., %)				< 0.001	0
Cardiac surgery	152 (25.9)	72 (16.5)	80 (52.6)		
Thoracic surgery	14 (2.4)	11 (2.5)	3 (2.0)		
Abdominal surgery	65 (11.1)	56 (12.8)	9 (5.9)		
Vascular surgery	22 (3.7)	15 (3.4)	7 (4.6)		
Orthopedic surgery	222 (37.8)	187 (42.9)	35 (23.0)		
Others	113 (19.2)	95 (21.8)	18 (11.8)		
Surgical risk (no., %)				< 0.001	0
Low	83 (14.1)	80 (18.4)	3 (2.0)		
Intermediate	263 (44.7)	206 (47.3)	57 (37.5)		
High	242 (41.2)	150 (34.4)	92 (60.5)		
Surgery duration (min.)	209.0 ± 121.7	188.9 ± 115.1	266.8 ± 121.9	< 0.001	0
Red blood cell transfusion (ml)	420.3 ± 1509.4	221.8 ± 575.5	972.4 ± 2705.7	< 0.001	66
Ventilation time (h)	13.9 ± 65.8	7.4 ± 13.4	32.2 ± 125.5	< 0.001	7
LOS in ICU (h)	56.8 ± 277.6	21.4 ± 62.4	159.3 ± 525.4	< 0.001	8
LOS in hospital (days)	19.3 ± 25.7	17.2 ± 25.7	25.6 ± 24.8	< 0.001	11

Data are mean (±) unless stated otherwise

POD postoperative delirium, *BMI* body mass index, *MoCA* Montreal Cognitive Assessment, *ASA* American Society of Anesthesiology, *NYHA* New York Heart Association, *rCRI* Revised Cardiac Risk Index, *MET* metabolic equivalent of tasks, *LOS* length of stay, *ICU* Intensive Care Unit

Table 2 Pre- and postoperative variables for the non-ICU and ICU stay

Characteristics	Non-ICU	ICU	*p* value
No	313 (53.2)	267 (45.4)	–
Duration in ICU	–	123.4 ± 399.4	–
POD (no., %)			< 0.001
Yes	36 (11.5)	113 (42.3)	
No	277 (88.5)	154 (57.7)	
Surgical discipline (no., %)			< 0.001
Cardiac surgery	4 (1.3)	148 (55.4)	
Thoracic surgery	6 (1.9)	8 (3.0)	
Abdominal surgery	31 (9.9)	31 (11.6)	
Vascular surgery	8 (2.6)	14 (5.2)	
Orthopedic surgery	183 (58.5)	36 (13.5)	
Others	81 (25.9)	30 (11.2)	
Surgical risk (no., %)			< 0.001
Low	75 (24.0)	8 (3 0)	
Intermediate	190 (60.7)	68 (25.5)	
High	48 (15.3)	191 (71.5)	
Surgery duration (min.)	140.9 ± 77.6	290.1 ± 114.9	< 0.001
Red blood cell transfusion (ml)	51.1 ± 277.4	856.0 ± 2136.6	< 0.001
Ventilation time (h)	3.6 ± 1.5	26.0 ± 95.7	< 0.001
LOS in hospital (days)	15.4 ± 20.6	24.0 ± 30.3	< 0.001

Data are mean (±) unless stated otherwise

POD postoperative delirium, *LOS* length of stay, *ICU* Intensive Care Unit

Table 3 POD as an independent predictor for LOS in ICU and in hospital: effects were adjusted for perioperative risk factors via a multivariable linear regression model and are presented as an increase in percent

	POD (adj. effect)	95% CI	*p* value
LOS in ICU (h)	1.36	1.04–1.78	< 0.001
LOS in hospital (days)	1.22	1.04–1.43	< 0.001

POD effect on LOS ICU adjusted for perioperative risk factors (preoperative age, ASA-, NYHA-, MET-, rCRI-classification levels, hearing impairment, history of delirium, number of medication and intra-/postoperative surgical risk, surgical discipline, duration of surgery, red cell blood transfusion, ventilation time). POD effect on LOS in hospital adjusted for perioperative risk factors (such as for the regression analysis for LOS ICU without ventilation time)

POD postoperative delirium, *CI* confidence interval, *ICU* Intensive Care Unit, *LOS* length of stay

POD is a multifactorial complication in which both preoperative predisposing factors as well as intraoperative and postoperative precipitating factors contribute to its development. Significant contributors to the development of POD are the duration time of surgery and the period of ventilation. Patients who developed POD showed a significantly longer operation time of 78 min on average, a longer ventilation time of 25 h and a longer stay in the intensive care unit of 138 h in this subgroup analysis. It should be noted here that outliers, especially in the POD group, influence the time values of ventilation duration and intensive care stay.

Relationship between ICU stay and POD development

The literature describes, in particular, the large influence of the ICU stays on POD. Due to this significant influence of the ICU stay, this cohort of the subgroup analyzed here was considered in more detail. According to the existing results in the literature, the patients with a subsequent ICU stay had a significantly longer operation time of 149 min more on average, a significantly larger amount of blood transfusion of 805 ml, and a longer ventilation time of 22 h. As mentioned above again a few outliers, especially in the ICU group, characterize the values for ventilation duration and transfusion volume. Furthermore, the results showed that the cohort of patients with an ICU stay also developed POD significantly more often than the opposite group. These results also confirm the findings of other studies that patients with an ICU stay are much more likely to develop POD [38–41]. Another observational study also looked at the occurrence of POD in the ICU and found that POD monitoring alone improved patient outcome [42].

Impact of POD on LOS in ICU and in hospital

There is various evidence in the literature that patients with a POD or ICU stay have a longer LOS in the hospital [3, 18, 19]. In this regard, we wanted to use this subgroup analysis to show more precisely whether the total length of hospital stay was influenced more by the fact of a necessary ICU stay or primarily by the secondary diagnosis of POD. Patients who developed POD had an average longer hospital stay of about 8 days. However, patients with an ICU stay had a longer average hospital stay of 9 days compared to patients without an ICU stay.

To test whether the occurrence of POD influences LOS in the ICU and in the hospital, a linear regression model was performed, risk-adjusted for perioperative risk factors in both cases. The results of our model showed that the development of POD resulted in a 36% increase in LOS in the ICU independent of perioperative risk factors. Furthermore, the results confirm that patients with POD had a 22% increase in-hospital LOS after risk adjustment. Confirming our findings, another study also found that POD is a robust predictor of LOS in ICU and also has a significant impact on the morbidity and mortality of patients undergoing surgery [43]. From these results, it can be concluded that POD has an independent impact on LOS in ICU and in hospital.

An intervention study addressed the problem of POD and prolonged ICU stay and found that a more extended ICU visit model can reduce both POD incidence and LOS [44]. Through the results of our analyses and the supporting findings of the literature, the importance of POD issues for elderly patients overall and specifically for ICU patients is demonstrated. Based on the known risk factors for POD and prolonged ICU stay, risk screening and interventions for prevention need to be further explored and applied in routine clinical practice.

Limitations

This study has several limitations. A limitation is that the positive delirium diagnosis is based on the results of the delirium tests and not on a diagnosis by a psychologist. Another limitation to be mentioned is that although the regression analysis has included certain risk factors for postoperative delirium, there may be other unobserved confounders. In addition, it has to be considered that the analysis carried out here is a subgroup that exclusively observes patients over 70 years of age.

Conclusions

The subgroup analysis presented here shows that POD has an independent and significant impact on LOS in ICU and in hospital. The occurrence of POD resulting in a prolongation of the inpatient stay could lead to an increased risk for further postoperative complications for the patient. Furthermore, the already limited resources regarding the availability of ICU beds and the workload of the clinic personnel are very much burdened by a prolonged length of stay. To avoid the scarceness of hospital resources it is of major importance to detect patients at risk for POD by adequate risk screening, so standardized screening in hospitals is necessary.

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3.4 Publication 4: Prä-Operative Prädiktion eines postoperativen Delirs durch geeignetes Screening (PROPDESC) – 21. Deutscher Kongress für Versorgungsforschung 2021

[540] Prä-Operative Prädiktion eines postoperativen Delirs durch geeignetes Screening (PROPDESC)

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Hintergrund

Mit einer Inzidenz von 11% - 51% ist das postoperative Delirium (POD) eine häufige Komplikation nach chirurgischen Eingriffen, die insbesondere die ältere Bevölkerung betrifft (1,2). Neben dem Alter stellen Multimorbidität, vermindertes Hör- und Sehvermögen, Immobilität und kognitive Dysfunktion ein erhöhtes Risiko für ein POD dar (3). Die kontinuierliche Zunahme der älter werdenden Bevölkerung und das erhöhte OP Aufkommen in dieser Altersgruppe (in 2019 53% der über 60-jährigen) bergen schon jetzt eine Herausforderung für das deutsche Gesundheitssystem (4). Trotz der teils schwerwiegenden Komplikationen, die das POD für die Patienten bedeuten kann (erhöhtes Mortalitätsrisiko, bleibende kognitive Schäden, Verschlechterung der Mobilität und Selbstständigkeit) und den belastenden Faktoren der krankenhausinternen Ressourcen (monetär wie auch organisatorisch), gibt es aktuell in deutschen Krankenhäusern noch kein standardisiertes Risikoscreening (5–7).

Primäres Ziel der prospektiven monozentrischen Beobachtungsstudie PROPDESC war es, ein möglichst prädiktives und klinisch einfach durchführbares präoperatives Screening Instrument zur Vorhersage des postoperativen Delir-Risikos durch klinische Routinedaten und kurzem kognitiven Screening zu evaluieren.

Methode

In die PROPDESC-Studie wurden von Sep. 2018 bis Okt. 2019 insgesamt 1097 Patienten mit einem Alter über 60 Jahre und einer geplanten Operationszeit von mindestens 60 Min. eingeschlossen. Die Delir-Testung erfolgte an 5 aufeinanderfolgenden Tagen mittels unterschiedlicher Assessment-Tools für die Normal- und Intensivstation. Basierend auf den präoperativ erhobenen Daten wurde an einer Evaluierungskohorte (n=600) ein Delir-Risikoscore entwickelt und auf einer weiteren unabhängigen Kohorte (n=378) intern validiert.

Ergebnisse

Die Delir-Inzidenz der gesamten Kohorte betrug 24%. Die präoperativ zu erhebenden Variablen zur Delir-Risikoeinschätzung (mit einer Staffelung von <10% - >50% Risiko) bestehen zum einen aus den Routine-Anästhesie Klassifikationen ASA, NYHA und OP-Risiko, sowie dem Alter und zwei einfach durchführbaren kognitiven Testungen aus dem Montreal Cognitive Assessment. Der hieraus entwickelte Delir-Risikoscore weist eine AUC von 0,725 (95% CI: 0.672 – 0.777) auf. Es konnte gezeigt werden, dass das Auftreten des POD einen unabhängigen signifikanten Effekt auf die Verweildauer im Krankenhaus und der Intensivstation hatte.

Diskussion

Der PROPDESC-Score wurde auf einer fachübergreifenden Kohorte eines Klinikums der Maximalversorgung entwickelt. Eine externe Validierung des Scores an Krankenhäusern aller Versorgungsstufen ist in Planung.

Implikationen

Der PROPDESC--Score ist einfach und zügig in der klinischen Routine anzuwenden und bietet für Krankenhäuser die Möglichkeit den Ressourceneinsatz zur Delir-Prävention in Verbindung mit den prozentualen Risikoabstufungen selbst zu wählen.

Appell

In Anbetracht der medizinischen wie ökonomischen Relevanz des Delirs ist die Durchführung eines deutschlandweiten standardisierten Delir-Risiko Screenings und einer darauf angepassten Prävention eine wichtige Herausforderung für die zukunftsorientierte Versorgung der alternden Bevölkerung.

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4. Discussion with references

The developed and internally validated PROPDESC score estimates POD based on age, ASA physical status, NYHA classification, surgery risk and short cognitive assessment (serial subtraction task and repetition of two syntactically complex sentence from the Montreal Cognitive Assessment (MoCA)). Based on routine clinical data and the two cognitive short tests, the PROPDESC score can be determined in a few minutes, as required by the ESAIC POD guideline (Aldecoa et al., 2017).

4.1 Strengths and weakness of the PROPDESC score

PROPDESC score was developed according to the scientific requirements for the development of a prognostic model of POD risk (Lindroth et al., 2018; Collins et al., 2015). The simplified score yielded an AUC of 0.725 on validation dataset. This result performed slightly below the prediction accuracy via bootstrapping on the development group (AUC of 0.767). Based on the strong focus for practical use in the clinical routine the simplified score was chosen because of lower number of variables (6 vs. 12 to 16) and less cognitive testing parts.

Compared with other POD scores, the predictive accuracy is lower, but most risk scores are based on perioperative data, such as the Delphi score of Kim et al. with an AUC of 0.94 in a retrospective study design (Kim et al., 2016; Lindroth et al., 2018). The development of POD is multivariate and thus it is explainable that a preoperative data set is weaker in predictive power than a data set with additional intra- and postoperative variables. Since the conservative approach to prevention begins preoperatively, it is necessary to identify risks as early as possible.

In terms of translational research (from bench to bedside and from bedside to practice), the choice of the simplified PROPDESC score is unquestionable. According to the “Throughput model” of health services research, it is not only important to use the right methods, but also to consider the personnel and organizational context (Schrappe and Pfaff, 2017). In conjunction with limited hospital resources, long-term implementation of a POD screening tool will only be successful if it is simple and quick to use.

4.2 Medical economic impact of POD

The results of the cardiac surgery subgroup analysis showed a substantial difference between the number of coded delirium diagnoses (ICD-10) and the actual POD patients tested positive. These results did not deviate from the Germany-wide average (InEK, 2019). According to the billing modalities of the Diagnosis Related Groups (DRG) catalogue valid at the time of the study, it can be deduced that for procedures with high material costs, the secondary diagnosis does not trigger a revenue-relevant increase in the PCCL and therefore also no increased billing amount. In 2017, the Institute for Quality Assurance and Transparency in Healthcare (IQTIG) final report confirmed the statement that POD is often not coded based on a lack of revenue-relevant effect (IQTIG, 2017). However, as the Gemeinsamer Bundesausschuss (GBA) addressed the importance of delirium prevention and treatment, the IQTIG quality contracts will established POD screening and staff training as a requirement for German hospitals.

As confirmed in the literature, subgroup analyses supported the effects of POD on LOS in ICU and hospital for the cardiac surgery patients and for the older patients aged 70 years and older (Salluh et al., 2015). An extended LOS puts a strain on the organizational resources of hospitals and, based on the requirements of the DRG catalogue, there is no refinancing of the additional resources used. In summary, POD is not only an adverse postoperative complication for patients, but also a challenge for hospitals in terms of medical economics.

4.3 Limitation

The PROPDESC study has limitations despite the observational study design. The POD diagnosis is not based on the gold standard but on different validated test instruments. The regression methods used have implemented POD risk factors and surrogate parameters, but there may be additional unobserved confounders.

4.4 Conclusion

POD has not yet received consistent consideration in the hospital community, either in terms of routine risk screening or in terms of potential billing-related

factors. Probably an adjustment of the DRG catalogue in conjunction with the future results of the IQTIG quality contracts would be a useful step to raise POD awareness. Because in addition to resource orientation, it is important to remember that each individual patient suffers from POD and the subsequent complications. We hope to contribute to translational research with the developed PROPDESC risk score.

4.5 Prospects

The developed PROPDESC risk score will be validated in a multicentre study across Germany. In conjunction with the IQTIG quality contracts, a long-term implementation of the PROPDESC score in the clinical routine of the participating hospitals is intended. Following the positive validation, a conservative intervention study to prevent POD is planned. In addition, further medical economic analyses of the present data set will be performed.

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